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Regenerative effects of some antioxidants after liver resection

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Abstract

In this mini review; Our aim is to draw attention to the regenerative effects of some natural or unnatural antioxidants (as beta carotene, silymarin, resveratrol and quercetin; as lactulose, bicyclol) after liver resection and to explain the mechanisms of these effects. Here, the pathophysiology or surgical procedure of liver resection, issues such as the rate of resection, its necessity and how to decide are not included in our subject.

Keywords: Some antioxidants, regenerative effect, liver regeneration

Introduction

Regenerative effects of natural antioxidants

Yilmaz et al. were reported that daily 5 % sun dried organic apricot (SDOA) supplemented diet (as beta carotene source) have shown beneficial effects on liver regeneration (LR) after partial hepatectomy (PH) in rats. [1]. Their another similar study reported that a daily 10 % SDOA supplemented diet and 100 mg/kg/day Silymarin extract accelerated LR [2]. On the other hand, it was reported that at a dose of 200 mg/kg/day for 10 days silymarin administration after PH did not contribute to the proliferative regeneration of the liver [3].

It is reported that, 30 mg/kg thymoquinone protects rat liver under ischemia-reperfusion (I/R) conditions against hepatic injury caused by PH. It enhances LR by preventing oxidative stress, enhancing antioxidant defense capacity and attenuating mitochondrial damage, endoplasmic reticulum stress and apoptosis [4]. Curcumin was orally administered to rats at 100 mg/kg/day (3 times before hepatectomy and once afterward). There was not determined enough increase in liver weight, mitotic index (MI), hepatocyte density, and perioperative administration. It was shown to have an inhibitory effect on cell cycle progression during LR [5]. In another study, it was administered at the same dose for a total of 7 days (before 3 and after days of PH), it decreases the apoptotic index (AI) and increases the MI and proliferation index (PI). It also inhibits the increase of malondialdehyde (MDA) levels while increasing superoxide dismutase (SOD) activity and glutathione (GSH) levels. Therefore, curcumin has a regenerative effect, proliferative and antiapoptotic properties [6]. Gozeneli et al. were reported that in rats thymoquinone and curcumin when orally administered at 100 mg/kg/day dose for 7 days, both of them have been showed positive effects on LR based on some biochemical tests (as arginase, ceruloplasmin, nitric oxide (NO), tissue plasminogen activator) and histological tests (as Ki-67, hematoxylin-eosin stain). Also it must be emphasized that thymoquinone has more effective than curcumin [7].

In rats, single-dose of 100 mg/kg intraperitoneally (i.p.) geraniol administration plays a crucial role on LR by increasing the expression of hepatocytes, Interleukin 6 (IL-6) genes and tumour necrosis factor alpha (TNFα), additionally, it was decreased the serum alanine aminotransferase (ALT) levels at a higher rate when compared to silymarin [8]. Rosmarinic acid shows potent antioxidant activity in vitro DPPH• (1,1- diphenyl -2-picrylhydrazine radical) antioxidant assay [9,10]. And also it was administered at a dose of 0.2 g/kg/day by oral route to mice (before 3 and after 10 days of PH), it was determined that proliferation of hepatocytes by stimulating the mTOR (mammalian target of rapamycin)/S6K (S6 protein kinase 1) pathway and increases the index of the liver to body weight [11]. Resveratrol as a natural

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antioxidant has anti-inflamatory and anticancer properties, it is a phytoalexin found specifically in grape and red wine [12,13]. In rats, daily 60 mg/day orally resveratrol administration (before 7 and after 3 days of PH), reduces NO levels significantly decreases MDA and IL-6 levels and increases GSH levels, and it may be use as prophylactic [14,15]. In a study, the regenerative effects of resveratrol at 30 mg/kg/day and melatonin at 10 mg/kg/day doses were compared; resveratrol and melatonin reduced oxidative damage, induced apoptosis and decreased proliferation. Although both increased regeneration, resveratrol has a potent antioxidant and a more protective effect on hepatocytes, but a weaker antiproliferative effect than melatonin [14]. In rats, at a dose of 15 mg/kg/day quercetin administration (before 3 and after 4 days of PH), it significantly increases the MI and PI and decreases the AI significantly. Besides, it reduces the increase in MDA, corrects the impaired antioxidant SOD activity and GSH levels. And also quercetin reduces hepatic vacuolar degeneration and therefore increases the mitosis of hepatocytes. These results are due to the antioxidant, antiapoptotic and proliferative features of quercetin, and it has positive effects on LR [16].

In another study, Urtica dioica oils were administered to rats orally at a dosage of 2 ml/kg/day for a total of 7 days, (starting 3 days prior to the PH). Biochemical (MDA, SOD, GSH) and histological (MI), proliferating cell nuclear antigen labeling (PCNA), AI, PI, transferase-mediated deoxyuridine triphosphate nick end-labeling assay results have shown that these oils enhance LR [17].

Allium sativum (garlic) has been used for centuries for treatments of heart disease, headaches and tumors [18]. Allium sativum extract protects liver microsomal membranes from lipid peroxidation-induced chemical and physical changes [19]. Allyl disulfide (a garlic extract) was administered to rats at a dosage of 30 µg/kg/day before and after PH operation for a total of one week. It significantly increases PI and decreases MDA. Therefore it may be say that allyl disulfide provides a protective effect on post-PH oxidative damage and increases LR capacity [20]. Green tea catechin extract contains especially epigallocatechin gallate and its derivatives, as well as caffeine. Green tea catechin extract was mixed into the drinking water of rats and given free access for 7 days before PH. It significantly increases liver weight/body weight ratio and the PCNA index, improves serum aspartate aminotransferase (AST) levels and decreases serum MDA levels. As a consequence, pretreatment of it improves liver damage and increases liver regeneration through its antioxidative and anti-inflammatory effects after massive hepatectomy (at 90% PH) [21].

On the other hand, farnesol is an isoprenoid found in orange peel and strawberries. In rats, at a dose of 250 mg/kg/day for a total of 2 weeks before PH, when liver tissue was evaluated by using PCNA and hematoxylin-eosin staining method, it has been shown that cause apoptosis induction (because of PCNA positive cell numbers decrease in the S phase and inhibit cell proliferation). Therefore, farnesol inhibits LR after PH, but this study suggests that farnesol is a good anticancer agent [22]. Lycopene is a carotenoid found in tomato and tomato products [23]. Lycopene was dissolved in olive oil and given orally to rats at a dosage of 4 mg/kg/day for 6 weeks before PH surgery and 1 week after surgery. It was determined that plasma ALT, AST, MDA, and NO's levels increase significantly and lower GSH and SOD levels. Therefore, lycopene increases oxidative stress after PH and negatively affects (like farnesol) on LR [24]. In rats at a dose of 100 mg/kg/day for 4 days before PH Hyptis fructicosa was applied, and liver tissue samples were evaluated by using PCNA. It may be surely says that the use of Fructicosa increases LR approximately 2.5 times than control group [25].

Geranium species contain many active ingredients (such as quercetin, gallic acid) which has antioxidant activity [26]. At a dose of 300 mg/kg/day, Geranium schiedeanum was administered intragastrically for 7 days after PH against the liver damage caused by ethanol in rats. It was shown that decreases the mortality rate, causes an increase in liver weight and DNA concentration. Therefore, it may be say that G. schiedeanum exerts is a hepatoprotective effect by restricting the harmful effect of ethanol during LR [27]. EGb 761, an extract of ginkgo biloba and contains quercetin, kaempferol and ginkgolide [28]. In rats, antioxidant activity has been shown by increasing catalase (CAT) and SOD activities [29]. EGb761 was administered i.p. to rats at a dose of 25 mg/kg/day for 3 days before PH. As a result of the study, it reduces the extent of tissue damage caused by free radicals and inflammation. Hence, it induces LR by reducing the extent of liver damage through its antioxidative and anti-inflammatory effects [30]. Aqueous suspension solution of carvacrol was administered as a single dose of 73 mg/kg i.p. before PH, it significantly increases MI and PCNA among histological parameters. Carvacrol reduces vacuolization, stimulates the proliferation of hepatocytes and thus causes a significant increase on LR [31]. It also demonstrates regenerative effect using the IL-6/STAT3(signal transducer and activator of transcription 3) pathway after PH [32].

30 mg/kg vitamin E (α-tocopherol) and 100 mg/kg vitamin C solution were given to rats 30 min before PH and 100 mg/kg and 600 mg/kg vitamin E was administered 24 hr before PH. Vitamin administration decreases apoptosis, increases DNA synthesis and increases PI. As a result, vitamins C and E have a positive role on LR by decreasing lipid peroxidation [33]. 15 days before and 2 days after PH oral route 4 ml/kg/day fish oil, 4 ml/kg/day olive oil and intramuscular (i.m.) route 100 mg/kg/day vitamin E were administered to rats in different groups. In all groups, the number of mitosis increases and MDA levels decrease. In the fish oil and vitamin E groups, GSH and SOD levels significantly increase, while NO levels significantly decrease. Accordingly, a higher rate of antioxidant activity was shown in these groups. It was determined that, the most effective substance on LR is fish oil and the least effective substance is olive oil [34]. However, another study showed that the application of vitamin E before PH reduces lipid peroxidation in the early period and delays LR [35]. Clinoptilolite is a type of natural zeolite crystal that can be synthesized in the laboratory. It was administered orally at a dose of 5 mg/kg twice a day, 10 days after PH. It significantly decreases plasma MDA, AST, ALT levels and remarkably increases SOD activity and GSH levels. Clinoptilolite application increases the antioxidant capacity after PH and is thought to have a regenerative effect [36].

Erythropoietin was administered i.p. as a single dose (4 U/g) 30 minutes before PH. It significantly increases liver weight, decreases ALT and AST levels, decreases vacuolization and increases mitosis of hepatocytes, and erythropoietin increases LR in a short time

[37]. In another study, erythropoietin was applied subcutaneously to rats at a dose of 3000 U/kg after PH. It decreases AST levels, increases relative liver weight, MI, double nuclei cell number, and PCNA ratio. As a result, it shows that high dose erythropoietin administration increases LR [38]. In addition, different doses of erythropoietin have been shown to increase regeneration and survival in rats that underwent hepatectomy at different rates [39]. Prostaglandin E1 at a dose of 1, 10 or 30 µg/kg was administered i.p. to rats before and after liver resection 3 times in total. This application reduces increasing serum endotoxin and IL-6 levels and increases hepatic DNA synthesis and also it improves hepatic damage, increases LR and survival [40]. Besides, Prostaglandin E_2 levels, increase in the regenerative liver after PH and these increases occur before the initiation of DNA synthesis, thus increasing the proliferation of hepatocytes, and supplementation of prostaglandin E2 exogenously increases liver regeneration [41].

Regenerative effects of unnatural antioxidants

Lactulose, a synthetic lactose derivative is used in hepatic encephalopathy, constipation, and adjustment of blood sugar levels [42]. Drinking water application containing 0.5 % lactulose to rats, it increases liver weight, MDA levels and SOD activity while decreasing AST levels. Additionally, it was significantly increasing regeneration markers such as PCNA and cyclin D1. Lactulose accelerates LR due to hydrogen-inducing bacterial fermentation. On the other hand, the application of antibiotics combined with lactulose reduces the regenerative effect owing to induces less amount of H_2 [43]. Bicyclol, a synthetic antihepatitis drug has antioxidative properties, it was given to rats 3 times by oral at a dose of 300 mg/kg before PH. According to the findings, bicyclol substantially increased MI and PI. Moreover it significantly decrease liver tissue MDA and serum ALT, total bilirubin levels, and fixed the impaired SOD and GSH levels [44].

Leflunomide is an immunosuppressive active ingredient used in the treatment of rheumatoid arthritis [45]. It was administered to rats at a dose of 10 mg/kg/day for 2 days after PH, it significantly reduces MDA, protein carbonyl (a protein oxidation product), and myeloperoxidase, (a marker of neutrophil infiltration). And also, it causes an increase in SOD and CAT enzyme levels which shows antioxidant activity. According to the Ki-67 nuclear antigen test, it causes an increase in the number of positive cells. A result, leflunomide increases LR due to its antioxidant activities and immunomodulatory effects [46].

Cerium nanoparticles showed an 11% increase in regenerative index (hepatocellular proliferation) compared to those that were not applied [47]. Exposed to hepatic I/R injury, at a dose of 150 mg/kg MESNA (2-Mercaptoethane Sulfonate) was administered twice i.p. both before ischemia and before reperfusion in rats. It decreases AST and ALT levels, myeloperoxidase activity (an indicator of neutrophil infiltration), MDA, and hepatic collagen, all of which increase after I/R. Also, it increases the decreased GSH levels and returns them to the pre-hepatic injury level. It has antioxidant activity thanks to the thiol group in its MESNA structure and protects the liver [48]. In another study, it was administered at a dose of 400 mg/kg 3 h before PH, during 30 min Pringle maneuver (a technique to stop bleeding during PH). It increases relative liver weight, significantly decreases AST and ALT levels, increases mitotic activity, improves oxidative stress markers (GSH, MDA, and SOD), and inhibits nuclear factor-kB activation. In conclusion; it has an increasing effect on LR, especially due to its antioxidative effects [49].

Conclusion

It has been understood that many antioxidants (much of them are ingredients of foods) have a positive effect on LR. Conducting such in vivo studies in more detail (at subcellular levels), revealing the mechanisms of action of antioxidants and shedding light on future generations will make a great breakthrough for humanity. Aim of this mini review is to provide brief information to those who will plan studies on this subject and to contribute to their projects to some extent.

Conflict of interests
The authors declare that they have no competing interests.

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