ISSN: 2574-1241
DOI: 10.26717/BJSTR.2018.06.001375
Mediha Canbek. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

Mini Rewiew Open Access

The Effects of Antioxidants on Liver Regeneration

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Received: July 02, 2018; **Published:** July 10, 2018

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Keywords: Liver Regeneration; Antioxidants; Partial Hepatectomy; Acute Liver Injury

Introduction

The liver is an important organ that supports vital functions, including absorption of metabolites from the intestines, regulation of glucose and lipid metabolism, biotransformation of xenobiotics, secretion of hormones and maintenance of osmotic balance, etc. Impairment of hepatic functions for any reason may lead to hepatic failure if not treated appropriately [1,2]. Involving many complex events at both cellular and molecular level, regeneration of the liver is usually divided into three phases [3]. The "early phase" is when the regeneration starts with a rapid proliferation of the liver cells. It represents hepatocytes transition from G0 phase to G1, where the number of newly expressed genes and level of genetic expression is greatly elevated. The "transition phase" represents the occurrence of mitosis where the cells pass through G1-SG2-M phases during the cell cycle [4]. The "termination phase" is the cells re-entrance into the G0 phaseafter a couple of cycles of division. TGF-β plays a key role in G1 phase by halting cellular proliferation in this phase. Integrin signaling is also known to be involved in this phase [5].

Surgical hepatic interventions for various reasons (e.g. tumor) lead to oxidative stress by disturbing freeradical antioxidant balance. Peaking of ALT levels within first 12 hours of 70% partial hepatectomy (PH)[6] elevated MDA levels and trough amounts of GSH within first 24 hours [7] shows that the amount of free radicals increases two folds and is further indicator of decreased free radical scavenger capacity of the liver[8]. Free radicals were reported to negatively influence regeneration process by triggering several signaling pathways [9]. Another model where the liver regeneration is well studied is the acute liver injury model induced by chemical substances like CCl_4, since normalization of AST and ALT elevation due to oxidativestress appear to be only possible by regeneration and healing of parenchymal tissue [10]. Several studies were performed to test the hypothesis that regenerative effect could be mounted by administering various antioxidants to overcome the negative influences of free radical on hepaticre generation. Silymarin, one of these wellknown hepatoprotective antioxidant is used as the positive control in many studies [11]. It is a polyphenolic flavonoid isolated from *Sylbum marianum (milk thistle)* composed of silychristin, silydianin, silybinin, and isosilybinin flavonolignans. Silymarin was reported to trigger regeneration in the early phase of hepatic regeneration induced by 70% partial hepatectomy [12,13]. Several studies demonstrated the efficacy of silymarin against acute liver injury [10, 14-16]. Nevertheless, Kabiri, et al. induced liver injury by thioacetamide and reported that no mitosis but largenucleated cells were seen in silymarin treated group [6]. Regenerative effect by silymarin was thought to be resulted from increasing DNA, RNA, and protein levels by acting as RNA polymerase [10,13]. Silybinin,one of the flavonolignans of silymarin, is the main component of silymarin [17]. Sonnenbichler and Zetl(1984) reported increased mitotic activity by silybinin in hepatocytes after partial hepatectomy [18]. Similar to that of silymarin [14] regenerative effect of silybinin is thought to be associated with IL-1 andTNF-α pathways [8]. Quercetin, a flavonoid found in many vegetables and fruits, is a useful antioxidant studies in various areas [19]. Quercetin (15mg/kg,orally,7 days) was reported to increase liver regeneration after partial hepatectomy, as measured by mitotic index [20]. Another study investigate dregenerative effect of quercetin (50mg/kg, 8 days) by inducing a Partial hepatectomy and CCl4 mediated injury, where it was reported to exert hepatoprotective effects with no cellular proliferative activity [19]. Iwao, et al. reported that quercetin (200mg/kg, i.p.) that was administered just after partial hepatec to my triggered apoptosis during early phase of regeneration [21]. These different effects of quercetin in the same model could be explained by several factors such as dose, way, and duration of administration, and that its effects are observed in different phases of partial hepatectomy [19]. Curcumin, a polyphenolic substance obtained from rhizome *Curcuma longa plant,* was reported increase GSH levels and inhibit lipid per oxidation [9,22]. In the study where its effect on regeneration was investigated by Partial Heptecto my model, curcumin (100mg/kg) was shown to inhibit regeneration in G2/M transition rather than G1/S transition [22]. Another study reported curcumin (100mg/kg for 7 days) to elevate GSH levels and exhibit

regenerative effect as measured by MI and PCNA analyses [9]. Resveratrol is a phytoalexin known for its antioxidant propertyand synthesized by the plants in case of stress. It was reported to show favorable effects on regeneration process both after 70% partial hepatectomy and liver injury triggered by CCl4 [23,24]. Baicalein is a flavonoid isolated from root extract of Scutellaria baicalensis Georgi; and its regenerativeeffect was demonstrated in CCl4-induced acute liver injury by PCNA, IL-6, and TNF-α analysis [25]. Geraniol, a monoterpenoid alcohol comprises volatile oil of some plants such as rose, lavender, and geranium. Itsantioxidant characteristic was reported in several studies. Canbek, et al. compared effects of geraniol (100mg/kg) and silymarin (100mg/kg) on liver regeneration, and reported that both substance similarly increased mitotic activity and exhibited regenerative effect in hepatocytes [26]. It was further suggested that this effect of geraniol could be attributed to IL-6 and TNF-α expression. Its regenerative effect (p.o. 100mg/kg, 200mg/kg) on liver was also reported by another study [27]. Carvacrol is a volatile oil extracted *Origanum onites L.* from. (thyme), and known to have antioxidant activity [28]. The study by Uyanoglu, et al. examined the effect of carvacrol on regeneration in PH model, where carvacrol+PH group had higherlevels of mitotic and PCNA indices compared to that of PH alone group at hour 72of PH, suggesting a regenerative effect of carvacrol [29]. Ternatin is a bioflavonoid isolated from flowering tops of *Egletesviscosa L*. (Asteracea) and has antihepatotoxic and antiinflammatory activity. Administered for 14 days at 0.1ml/kg i.p. dose to rats, its effect was examined in different timepoints in post PH regeneration setting (36h, 168h, 336h). It was reported that GSH level was markedly reduced at hour 168, and it had no effect on hepatic regeneration [30]. Melatonin is an endogenous antioxidant secreted from pineal gland and known to exert activity on regeneration. The study by Abbasoglu, et al. (1995) reported negative effects on liver regeneration in rats whose pineal glands were removed [31]. Beside its many vital functions, liver has a high regeneration capacity. Removal of a part of the liver for any reason or its transplantation or acute liver injury may lead to oxidative stress injury having the potential to negatively affect regeneration process. Regenerative medicine is important for replacement of injured tissue with the function alone [32,33]. Antioxidants seem to make contribution to regenerative medicine.Nonetheless, we believe that better understanding of their effects on liver regeneration warrants further comparison of these antioxidants with each other including different dosages, routes of administration and duration. Moreover, advanced molecular studies will further shed light into their modes of action.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.06.001375

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