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The Effects of Antioxidants on Liver Regeneration

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Introduction

The liver is an important organ that supports vital functions, including absorption of metabolites from theintestines,regulationof glucose and lipid metabolism, biotransformation of xenobiotics,secretionofhormonesand maintenance of osmotic balance, etc. Impairment of hepatic functions for any reason maylead to hepatic failure if not treated appropriately [1,2]. Involving many complex events at both cellular andmolecular level, regeneration of the liver is usually divided into three phases [3].The "early phase" is whenthe regeneration starts with a rapid proliferation of the liver cells. It represents hepatocytestransition fromG0 phase to G1, where the number of newly expressed genes and level of genetic expression is greatlyelevated. 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 cellsre-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 thisphase. 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 or 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 24hours [7] shows that the amount of freeradicals increases twofolds 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 signalingpathways [9].Another model where the liver regeneration is wellstudied is the acute liver injury modelinduced 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 byadministering various antioxidants to overcome the negative influences of free radical on hepaticregeneration. Silymarin, oneof these wellknown hepatoprotective antioxidantis used as the positivecontrol in many studies [11]. It is a polyphenolic flavonoid isolated from Sylbummarianum(milkthistle)and composed of silychristin, silydianin, silybinin, andisosilybinin flavonolignans. Silymarin was reportedto 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 butlargenucleated cells were seen in silymarintreated group [6].Regenerative effect by silymarin was thought tobe resulted from increasing DNA, RNA, and protein levels by acting as RNA polymerase [10,13]. Silybinin,one of theflavonolignans 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 antioxidantstudies in various areas [19]. Quercetin (15mg/kg,orally,7 days) was reported to increase liverregeneration after partial hepatectomy, as measured by mitotic index [20]. Another study investigatedregenerative effect of quercetin (50mg/kg, 8 days) by inducing a Partial hepatectomy and CCl4 mediatedinjury, 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 hepatectomytriggered apoptosis during early phase of regeneration [21].

These different effects of quercetin in the samemodel could be explained by several factors such as dose, way, and duration of administration, and that itseffects are observed in different phases of partial hepatectomy [19]. Curcumin, a polyphenolic substanceobtained from rhizome extract of Curcuma longa plant, was reported increase GSH levels and inhibit lipidperoxidation [9,22].In the study where its effect on regeneration was investigated

by Partial Heptectomymodel, curcumin (100mg/kg) was shown to inhibit regeneration in G2/M transitionrather than G1/Stransition [22]. Another study reported curcumin (100mg/kg for 7 days) to elevate GSH levels and exhibitregenerative effectas measured by MI and PCNA analyses [9]. Resveratrol is a phytoalexin known for itsantioxidant propertyand synthesized by the plants in case of stress. It was reported to show favorableeffects 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 alcoholcomprises 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 liverregeneration,and reported that both substance similarlyincreased mitotic activity and exhibited regenerative effect in hepatocytes [26].

It was further suggestedthat 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 extractedfrom Origanum onites L. (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 aregenerative 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 at0.1ml/kg i.p. dose to rats, its effect was examined in different timepoints in postPH regeneration setting(36h, 168h, 336h). It was reported that GSH level was markedly reduced at hour 168, and it had no effecton hepatic regeneration [30].

Melatonin is an endogenous antioxidant secreted from pineal glandandknown to exert activity on regeneration. The study by Abbasoglu, et al. (1995) reported negative effects onliver 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 anyreasonor its transplantationor acute liver injury may lead to oxidative stress injuryhaving the potentialto 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 furthercomparison of these antioxidants with each other including differentdosages, routes of administrationandduration. Moreover, advanced molecular studies will further shed light into their modes of action.

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