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Protective effects of plant-derived flavonoids on hepatic injury

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ABSTRACT

Liver ailments have become one of the most health-threatening problems, looking for safe and effective natural liver protection agents is one of future directions. Flavonoids are widely found in traditional Chinese medicinal (TCM) herbs, some of which have significant protective effects on liver injury caused by various factors. From the recent research progress, it is concluded that flavonoids can enhance the antioxidant functions of liver by increasing the level of superoxide dismutase, glutathione s-transferase and glutathione peroxidase, improve insulin sensitivity and inhibit hepatic stellate cell activation by regulating the activities of the enzymes such as heme oxygenase-1, cytochrome P450 and telomerase, reduce inflammatory reaction by restraining the expression of tumor necrosis factor-α, interferon-γ and interleukin-6, and mediate apoptosis and autophagy by controlling the pathways of genes-p 53-genetics, nuclear factor κB and phosphatidylinositol 3-kinase/protein kinase B signaling, which will provide an alternative way for the treatment of liver injury.

1. Introduction

The liver is not only for metabolism and detoxification, but also with superior innate immune function, which is helpful to the antivirus, antibiosis and antitumor in the liver (Gao, Jeong, & Tian, 2008). Many substances such as alcohol and drugs attack hepatocyte to produce a series of mediators including inflammatory factors and cytokines, cause the necrosis, apoptosis, inflammation and fibrosis of liver (Gu & Manautou, 2012; Tsukamoto & Lu, 2001), resulting in liver damages (Fig. 1). Once liver was damaged, it would lead to metabolic disorders such as lactic acidosis (Pellegrinotti, Fimognari, Franco, Repetto, & Pastorelli, 2009), hypoalbuminemia and fat malabsorption (Rezaeian, Ghayebi, Moghadam, & Shajari, 2014). Liver injury is becoming widespread owing to the high-frequency occurrence of food and drug safety issues and occupational or environmental exposures to heavy metals (Andrade et al., 2005; Garcíaniño, & Pedrazachaverrí, 2014).

Liver protecting agents aim to improve hepatic metabolism, enhance liver detoxification function and promote the regeneration of hepatocyte. At present, the commonly used liver protective drugs, such as tiopronin, glutathione and biphenyl dimethylester, are mostly chemical-based drugs that might have side-effects. For instance, potential risk of liver injury exists with long-term tiopronin treatment (Zheng et al., 2014), and a combination of pegylated interferon-α (IFN-α) and ribavirin only has long-term effect on 50–60% hepatitis C patients (Sarasin-Filipowicz et al., 2008).

Traditional Chinese medicinal (TCM) herbs contain a lot of active ingredients, which have therapeutic effects on many diseases with little side effects (Normile, 2003; Tsai, 2001). Flavonoids are a class of natural phenolic compounds widely found in TCM herbs such as *Scutellaria baicalensis*, *Scutellaria barbata*, and *Capparis spinosa* (Mollica et al., 2017; Niu et al., 2015; Zhang et al., 2018). Flavonoids have antioxidant, anti-virus, anti-inflammatory and many other biological activities (Emerit et al., 2005; Goya, Sarriá, Ramos, Mateos, & Bravo, 2016; Sánchez-Roque et al., 2017; Zengin et al., 2017). Some of flavonoids have remarkable therapeutic effects on liver injuries caused by various factors like alcohol, drugs, chemicals (Albano, 2008; Ma, Wang, & Jiang, 2016; Mitchell, Snodgrass, & Gillette, 1976). The hepatoprotective effect of flavonoids may be related to its effective antioxidant and anti-inflammatory activities (Wu et al., 2006). The protective effect of flavonoids on liver injury works by a variety of pathways, and many reports have been reported in recent years. In this review, we summarize the flavonoids with protective effects on liver injury and their sources, molecular structures and action mechanisms.

2. Protective effects of flavonoids on liver injury

The benzene rings A and B in flavonoids could be replaced by substituent group such as phenolic hydroxyls, O-sugars, methoxy

Abbreviations: ATGL, adipose triglyceride lipase; D-GaIN, D-galactosamine; FLIP, FLICE inhibitory protein; HA, hyaluronic acid; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LN, laminin; MPO, myeloperoxidase; NO-cGMP, nitric oxide–cyclic guanosine monophosphate; PC, procollagen type; PXR, pregnane X receptor; RNS, reactive nitrogen species; SGPT, serum glutamate pyruvate transaminase; T-AOC, total antioxidant capacity; T-BILI, total bilirubin; TG, triglyceride; TOR, target of rapamycin

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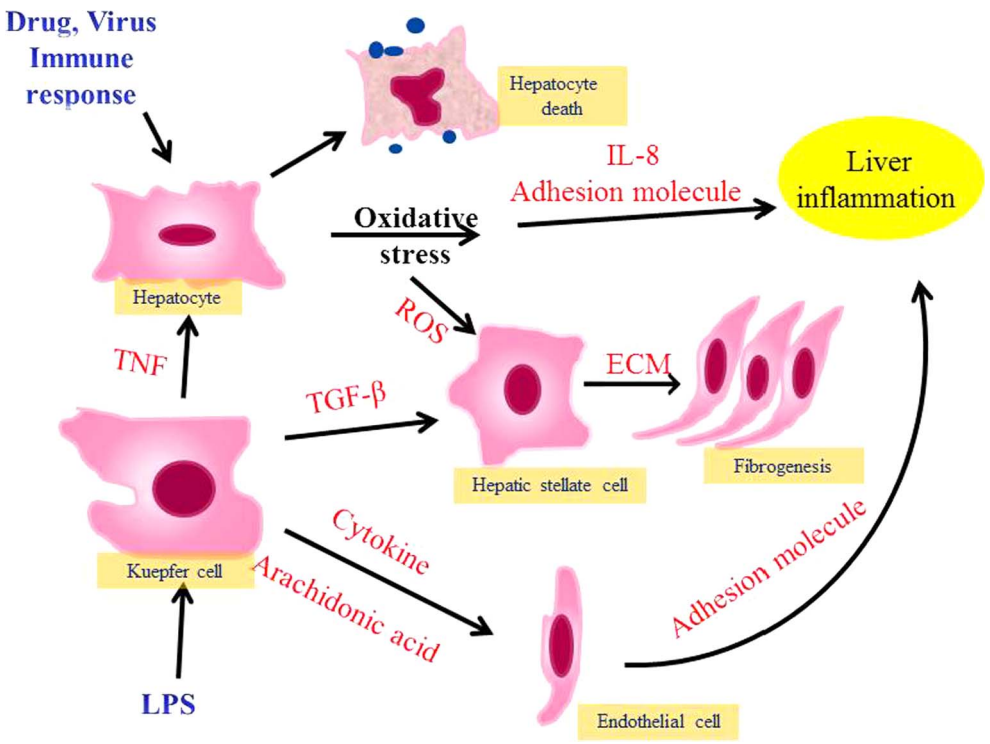

Fig. 1. Interaction of liver cells in liver injury. There are four kinds of cells in liver: hepatocyte, Kupffer cells, stellate cells and endothelial cells. These cells produce various chemical mediators through paracrine and autocrine to transfer information, interaction. Various kinds of harmful factors and substance, such as viruses, drugs, alcohol, and immunity, use one or more cells as target cells. It stimulates cell damage, producing a series of media, causing changes in cell necrosis and apoptosis, inflammation, fibrosis and pathology, resulting in various liver diseases. LPS, lipopolysaccharide; ROS, reactive oxygen species; IL-8, interleukin 8; TNF, tumor necrosis factor; TGF-β, transforming growth factor; ECM, extracellular matrix.

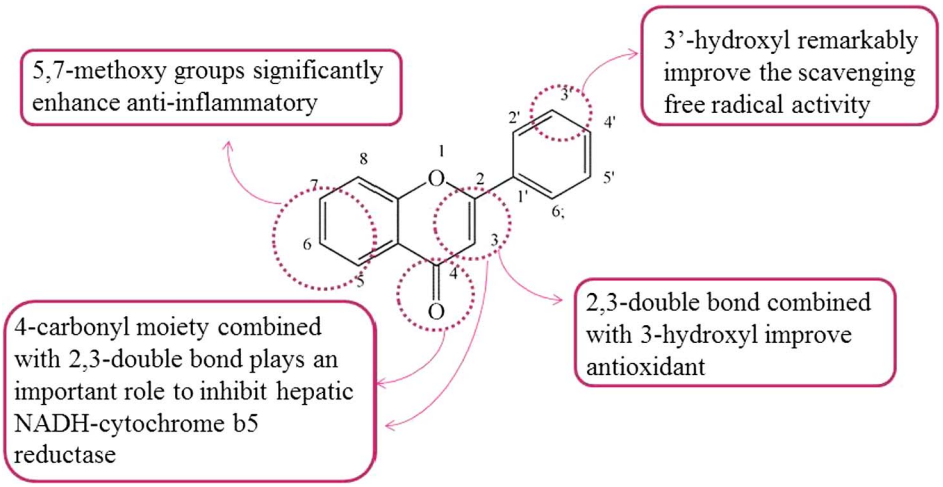

Fig. 2. The key function related with different chemical groups.

groups, sulfates and glucuronides (Hollman & Katan, 1999). Studies had shown that the number and position of substituent group in flavonoid rings affect their antioxidant effects and the capacity to act as modulators of enzymes (Çelik & Koşar, 2012; Mendes, Borges, Neto, Macedo, & Silva, 2012). 3-hydroxyflavone is the basic antioxidant structure for the simplified flavonoids; the scavenging free radical activity closely related to C-3′-hydroxyl group, to some degree, increase with the number of hydroxyl groups on B ring. A carbonyl group at C-4 in combination with a double bond between C-2 and C-3 may produce a much stronger inhibition on hepatic NADH-cytochrome b5 reductase. The anti-inflammatory activity decreased with the number of methoxy groups (Fig. 2), but it becomes much stronger when the methoxy groups is located on C-5 and C-7 (Çelik & Koşar, 2012; Husain, Cillard, & Cillard, 1987; Loggia, Sosa, Tubaro, & Bombardelli, 1993; Mendes et al., 2012; Zhu, 1998).

2.1. Protective effects of flavonoids on chemical liver injury

Chemical liver injury (CLI) is caused by some drugs or toxic substances in the environment (Mitchell et al., 1976). The liver is easily damaged by chemicals to which we are ubiquitously exposed. Chemicals entering human body first produce harmful intermediates such as electrophilic compounds or free radicals which can potentially induce oxidative damage or alter the structure and function of cellular macromolecules. The effects of reactive intermediate species might lead to deregulation of cell signaling pathways and dysfunction of biomolecules, when protective defenses are overwhelmed by excess toxicant insult, resulting in failure of target organelles and eventual cell death (Gu & Manautou, 2012).

Drug-induced liver injury (DILI) is a seriously side effect caused by clinical drug including isoniazid, augmentin, trimethoprim/sulfamethoxazole and phenytoin, which is a great threat to patients health (Chang & Schiano, 2007). A large number of the clinical cases of DILI were resulted from overdose of acetaminophen (APAP), one of