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Review

Essential role of nuclear receptors for the evaluation of the benefits of bioactive herbal extracts on liver function

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ABSTRACT

Nuclear receptors (NRs), ligand-dependent transcription factors, play important regulatory roles in diverse metabolic processes including hepatic lipid, glucose and bile acids (BAs) metabolism involved in liver and metabolic disorders. Therefore, NRs are attractive targets for treatment or prevention of liver diseases. However, the cost-effectiveness and safety of currently available synthetic NRs agonists or antagonists are under question. Herbal extracts and their derivatives with superior cost-effectiveness and less toxicity have attracted much attention as the potential option for NRs agonists or antagonists. Several herbal extracts have been reported to regulate NRs level and exert hepatoprotective property through increasing fatty acid β-oxidation, preventing hepatic BAs, cholesterol and lipid accumulation. Mechanistically, those herbal extracts have regulatory effect on NRs and subsequently alter their target gene cytochrome P450s (CYPs) level involved in the pathophysiology of liver diseases, which positively suggests that herbal extracts are valuable source of promising candidates for the prevention or treatment of liver diseases. This review highlights recent knowledge to discuss the benefits of bioactive herbal extracts on liver function through regulating NRs-dependent transcriptional activities of CYPs, collecting available studies on the herbal extracts with NRs-regulatory effect and the underlying mechanisms.

1. Introduction

The liver has the capacity to maintain bile acids (BAs) homeostasis and control lipid/glucose metabolism with multiple enzymatic pathways. Therefore, abnormal BAs metabolism can break the homeostasis and lead to an excessive accumulation of BAs retention in the liver associating with liver injury, eventually leading to cholestatic liver disease [1,2]. Fatty liver disease is a cause and a result of metabolic disorders ranging from neutral lipid accumulation (mainly as triglyceride) to the development of hepatic steatosis and fibrosis can eventually lead to cirrhosis. According to the etiology, alcoholic liver disease (ALD) is caused by chronic and excessive alcohol consumption, whereas nonalcoholic fatty liver disease (NAFLD) is diet-induced excessive lipid accumulation in liver cells leading to an imbalance of pathways involved in fatty acid and triglyceride, and closely associated with obesity, insulin resistance and diabetes [3]. Currently, NAFLD is a prevalent problem in 25.24% of the global population, and approximately 40.76% of the patients with NAFLD progress to nonalcoholic steatohepatitis (NASH) and liver failure [4,5]. Moreover, liver plays a key role for metabolizing and eliminating xenobiotics and prevention against the absorption of toxic chemicals into the systemic circulation. Sometimes treatment with drug in a higher dose or for a longer period might lead to liver exposure to xenobiotics continuously, ultimately causes liver failure [6,7].

Nuclear receptors (NRs), a superfamily of ligand-activated transcription factors, commonly possess a large variety of ligands, including

Abbreviations: AHR, aryl hydrocarbon receptor; ALD, alcoholic liver disease; BAs, bile acids; CAR, constitutive androstane receptor; CARM1, coactivator associated arginine methyltransferases 1; CBP/P300, CREB-binding protein/p300; CYP27A1/Cyp27a1, sterol 27α-hydroxylase; CYP7A1/Cyp7a1, cholesterol 7α-hydroxylase; CYP8B1/Cyp8b1, sterol 12α-hydroxylase; DBD, DNA binding domain; DCA, dicarboxylic fatty acids; ERR, estrogen-related receptor; FGF/Fgf, fibroblast growth factor; FXR, farnesoid X receptor; GSP, Grape seed proanthocyanidins; LBD, ligand binding domain; LXR, liver X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NRs, nuclear receptors; PGC-1α, proliferation-activated receptor gamma coactivator 1-alpha; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RA, retinoic acid; RAR, retinoic acid receptor; ROS, reactive oxygen species; RXR, retinoid X receptor; SHP/Shp, small heterodimer partner; SRC, steroid receptor coactivator; SREBP-1, csterol regulatory element binding protein-1c; VDR, vitamin D receptor; TAA, thioacetamide; TZD, thiazolidinedione; WT, wide type

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steroid hormones, fatty acids, BAs, cholesterol, vitamins, and drugs/xenobiotics [8,9]. NRs are identified to mediate a series of hepatic lipid, lipoprotein and glucose metabolism as well as xenobiotic/drug disposition in distinct metabolic pathways, involving in the pathogenesis of obesity, hepatic insulin resistance, type 2 diabetes, cholestasis, hepatic steatosis, ALD and NAFLD as well as liver regeneration and tumor growth [10–14]. Therefore, NRs play critical roles in various liver physiology and pathobiology and open novel therapeutic targets for addressing a range of liver diseases, possibly also including their complications such as steatohepatitis, fibrosis-cirrhosis and hepatocellular cancer (HCC). Currently, there are many NRs agonists or antagonists that are going through Phase II or later stages of clinical trials with promising results. However, the cost-effectiveness and safety profiles of currently available NRs agonists or antagonists in patients are under question [15–18]. Thus, novel and effective alternative therapies with superior cost-effectiveness and a lower toxicity for liver diseases management are urgently needed. Herbal extracts have been gaining growing attention as one of the best approach for the discovery of new therapeutic molecules due to their multi-target, multi-mechanism of action as well as low cost and less toxicity profiles [19–21]. It is well known that Veregen (a green tea leaves extract) and Crofelemer (a botanical polymeric proanthocyanidin) have been approved by the US Food and Drug Administration for the treatment of condyloma and chronic diarrhea in patients living with HIV/AIDS, respectively [22,23]. In Asian countries, herbal extracts has been used as a common clinical practice for long to prevent against various liver diseases [24]. In the past decades, a series of clinical trials focused on characterizing the biochemical processes linking the effects of herbal extracts with the improvement of liver diseases [25,26]. Among those bioactive herbal extracts, which regulating NRs expression and activity can be considered as attractive therapeutic avenues for liver diseases [27,28].

It is interesting to note that NRs have been found to mediate the activities of herbal extracts by targeting cytochrome P450s (CYPs), which function as the major targeting genes of NRs involved in the pathways of hepatic metabolism of BAs, lipids, and glucose [29–32]. In general, CYPs as the most important phase I drug-metabolizing enzyme control the levels of diverse xenobiotics and endogenous substrates such as steroids, eicosanoids. Studies indicate that significant changes occur in the expression and activity of hepatic CYPs (especially for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) during the pathogenesis of fatty liver disease states such as ALD, NAFLD and NASH in humans and animals by regulating lipid peroxidation, fatty acid β-oxidation, oxidative stress and reactive oxygen species (ROS) generation [33,34]. For example, increased expression and activity of CYP2E1 protein are found to promote the progression of NAFLD [35,36]. In addition, the upregulation of Cyp4a10 and Cyp4a14 was observed in Cyp2e1-deficient mice with diet-induced NASH but not in wild-type mice. These Cyp4a enzymes act as alternative initiators of oxidative stress via active generators of ROS and catalyzing lipid peroxidation in the liver when Cyp2e1 was absent [37]. To date, a growing number of data indicate that many herbal extracts influence the protein expression of CYPs by interacting with NRs signalling pathways, implying that NRs-CYPs axis provide a novel therapies for liver diseases [38,39]. Therefore, the aim of this review is to summarize the current available experimental and clinical findings regarding herbal extracts with NRs regulatory effects used to prevent or treat liver diseases and discuss their underlying mechanisms.

2. The nuclear receptor superfamily

NRs, consist of 48 family members in humans and 49 in mice, which can be categorized into three major subfamilies according to their potential functions and the features of ligands [14]. The first class is endocrine receptors, which have a high affinity with fat-soluble ligands such as hormones and vitamins. Members of this class include androgen receptor, estrogen receptor, retinoic acid receptor (RAR), vitamin D receptor (VDR) and so on. Targeting endocrine receptors as novel strategies are very successful in daily clinical practice [40,41]. The adopted orphan receptor is the second subfamily, which were identified to share a similar sequence with endocrine receptors. At first, their natural and endogenous ligands were unknown. Therefore, these receptors were termed “adopted orphan receptors”. This class of NRs includes pregnane X receptor (PXR), farnesoid X receptor (FXR), liver X receptor α/β (LXRα/β), peroxisome proliferator-activated receptor α/γ/δ (PPARα/γ/δ), and retinoid X receptor α/β/γ (RXRα/β/γ). This class of NRs participates in lipid and/or glucose homeostasis by regulating the uptake, synthesis, storage and excretion, which make these NRs into the most potential drug targets for metabolic diseases in clinical use [42,43]. Another subtype of adopted orphan receptors, called enigmatic orphan receptors, for which a ligand has been recognized, but ligand-dependent regulation has not yet been established. Receptors of this class include such as RAR-related orphan receptors, human liver receptor homologue-1, hepatocyte nuclear factor and constitutive androstane receptor (CAR). Given CAR could be activated by a variety of natural or synthetic ligands in different animal models, it may be harnessed for potential drug targets in managing a wide spectrum of metabolic diseases [44]. Orphan receptors are classed as the third subfamily whose structure has a highly homologous with the other subfamily, but whose natural ligands have not yet been known. Therefore, these receptors were defined as “true orphan receptors”. [45].

Generally, NRs have a central DNA binding domain (DBD), which is compromised of two highly conserved zinc-finger motifs that target distinct recognition sites on the DNA, and a functionally unique C-terminal ligand binding domain (LBD) capable of binding to specific DNA response elements of target genes, dimerizing receptor, and interacting with coregulator [46] (Fig. 1). In most cases, a conformational change in the activation function 2 region (AF-2) in LBD is essential for ligand-dependent interactions with transcriptional co-regulators, which initiates the dissociation of co-repressors including silencing mediator of retinoic acid and thyroid hormone receptor/nuclear receptor co-repressor 2 (SMRT/NCoR2) and recruitment of various coactivators [47]. After this exchange of co-regulators, RNA polymerase II is also recruited to the NR/DNA complex, finally resulting in transcription of target genes. In the presence of ligand, the RXR as a dimerization partner is capable of binding to NRs in a sequence-specific DNA recognition manner and forming solution homodimers or heterodimers, leading to the receptors switching from inactive to active and transactivating several specific elements in the 5-upstream regulatory region of the target genes, such as CYPs [32,48]. In the absence of ligand, NRs are either located in the cytoplasm, or in the nucleus, keeping inactive by forming a repressive complex with corepressors [49] (Fig. 2).

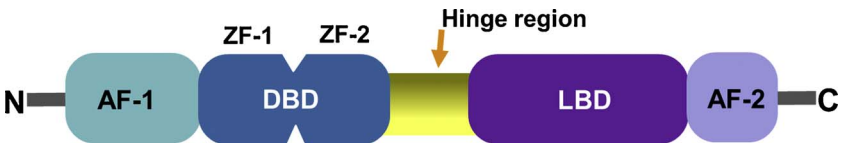

Fig. 1. Schematic diagram for a typical domain structure of NRs which generally composed of N-terminal activation function 1 (AF-1), transactivation domain, a conserved DNA binding domain (DBD) consisting of two zinc fingers (ZF), nonconserved hinge-region, a ligand binding domain (LBD), and a C-terminal region containing the ligand-dependent activation function 2 (AF-2) helix.