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REVIEW

Liver immunology and herbal treatment

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Abstract

Beyond the metabolic functions, the liver recently has been defined as an organ of immune system (IS), which have central regulatory role for innate and adaptive immunity. The liver keeps a delicate balance between hepatic screening of pathogenic antigens and immune tolerance to self-antigens. Herbal treatments with immunological effects have potential to alter this hepatic immune balance towards either therapeutic side or diseases side by inducing liver injury *via* hepatotoxicity or initiation of autoimmune diseases. Most commonly known herbal treatments, which have therapeutic effect on liver and IS, have proven *via in vitro*, *in vivo*, and/or clinical studies were summarized in this review.

Key words: Herbal treatments; Hepatic immunology; Drug induced liver injury; Adaptive immunity; Innate immunity

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Core tip: Herbal treatment is the mother of modern medicine. The ancient habit of treating diseases with plants still goes on as either primary or complementary to conventional medical treatment. The other side of medallion is the fact that the liver is number one target organ for herbal toxicity. Furthermore, liver has been recently defined as an active organ of immune system, which have central regulatory role on innate and adaptive immune response. The delicate homeostasis between immediate and efficient defense against threats (immune surveilance of antigens) without triggering harmful immune response towards self-structures (periferal immune tolerance to self antigens) is controled by liver. Herbal formulas are not a single plant extract, but is an interacting mixture of ingredients that determines the final clinical outcome as therapeutic and hepatotoxic effect. This review aimed to drive attention on both potentials of herbals from the point of immunology, in order to initiate a motivation for feature studies defining

the mechanisms of immunological interaction between herbals and liver.

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INTRODUCTION

Herbal treatment is the mother of modern medicine. Because of cultural, economical and practical reasons, the ancient habit of treating diseases with plants still goes on as either primary or complementary to conventional medical treatment. The other side of medallion is the fact that the liver is number one target organ of herbal and dietary supplements (HDS) induced toxicity. The Food and Drug Administration (FDA) under the Dietary Supplement Health and Education Act (DSHEA) regulate herbal treatments since 1994[1]. The submissions of new herbal products to FDA require the dose and list of ingredients to be written on its bottle, however, documentation of safety and efficacy is not need to be reported. Furthermore, HDS can be obtained without prescription, medical advice or monitoring. Although the actual size of the problem is not well defined, HDS-induced hepatotoxicity accounts for 20% of cases of hepatotoxicity in the United States and the rates differ from 2.5% in India to 70% in Singapore[2].

The liver is prone to drug-induced liver injury (DILI) because of its functions on metabolizing chemicals and regulating immune response. DILI can develop either by dose related direct drug toxicity, or - much more commonly - as idiosyncratic reactions due to individual susceptibility to ingredients. The complex composition of HDS eases the both direct toxicity and idiosyncratic reactions during their metabolism in liver. Idiosyncratic DILI (IDILI) is in most instances characterized by a mild injury (ALT < 3 times upper normal limit) which normalized with continuous drug treatment. This phenomenon of clinical adaptation is a biochemical adaptive response of organelles such as endoplasmic reticulum and mitochondria metabolizing chemicals. It is hypothesized that defective clinical adaptation mechanisms result in severe IDILI with jaundice and liver failure, in < 0.1% population with susceptible human leucocyte antigen (HLA) type. Microbiota is the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space[3]. The microbiota of gut also determinates IDILI susceptibly by regulating hepatic immune-tolerance though lipopolysaccharides (LPS) induced T-cell response in liver. According to theory, haptens of metabolized chemicals covalently bind to proteins, and become antigenic peptides. While 70%-90% of population has immune tolerance, the rest develop adaptive immune response due to their susceptible type HLA and/or dysfunctional microbiota. If biochemical adaptation mechanisms cannot control this initiated mild injury, acute liver failure develops[4]. There are supporting evidences to this theory. The many top IDILI drugs are antibiotics changing the normal microbiota. The "immune check point therapy" for cancer treatments are FDA approved antibodies that aim to inhibit T cell immune-tolerant states, such as ipilimumab (anti-CTLA4), pembrolizumab (anti-PD-1) and nivolumab (anti-PD-1). The major side effect of these treatments is to make individuals to susceptible to haptens (so inducing IDILI) and auto-antigens (so inducing autoimmunity).

This review aimed to drive attention on both therapeutic mechanisms and hepatotoxic potentials of herbal treatments from the point of immunology. After defining basic immune system (IS), we summarized the role of liver as an immune regulatory organ and then the herbal treatments with therapeutic potential on liver.

IS

IS has evolved to recognize and eliminate internal insults (*i.e.*, cancer cells) or external invading pathogens (*i.e.*, infections) by developing local or systemic response. IS composed of "classical lymphoid organs"; thymus, bone marrow, spleen, tonsils, lymph nodes and "peripheral immune organs"; skin, respiratory and gut mucosa-associated lymphoid tissues, adrenal glands. Additionally, the gut and liver are recently defined as active organs of IS. Although the primary functions of liver parenchymal cells are methabolical, they also carry out essential immune tasks. Beside all metabolic functions, liver has important role as an organ of IS.

IS begins to develop during intrauterine life. However, maturation of IS depends on antigenic stimulations from environment. The gut microbiota is initiated by maternal microorganisms gained during passage through birth channel and it dynamically change according to external conditions. The gut microbiota is necessary for proper "education" of IS. Although IS completes its maturation around teenage, lifelong antigenic stimulations from microbiota is needed for normal functioning of IS. Epidemiological observations and then, experimental data from germ-free animals leads to "hygiene hypothesis" and its modern extension called "microflora hypothesis". According to these hypotheses, the higher levels of cleanliness and decreased exposure to microorganisms (driven by factors such as antibiotic use, xenobiotics, infection, or diet) during early childhood disrupt maturation if IS. In other words, the dysbiotic gut microbiota, which arisen during critical window of IS maturation, turns the differentiation of naïve immune gut dentritic cells (DCs) from generation of Treg (regulatory) cells by tolerogenic DCs into generation of effector T cells by immunogenic DCs. This shifts TH response from Th1 type (IFN-γ mediated) to Th2 type (IL-4 mediated). As a result, the risk for autoimmune and allergic diseases increases[5,6].

By definition IS has 2 parts; the innate IS and the adaptive IS. Although this division simplifies the understanding of immune processes, IS orchestrates

whole immune cells during local or systemic responses.

Innate IS

The innate IS initiates first defense against insults, and is characterized by its ability to distinguish self from non-self. Its members are classic immune cells such as polymorphic nuclear leukocytes (neutrophils), monocytes, macrophages and DCs, natural killer (NK) cells, and innate lymphoid cells (ILCs), beside epithelial, endothelial and mesenchymal cells which are non-immune cells.

The inflammation during innate immune response is triggered by pattern-recognition receptors (PRRs). The 3 families of PRR, according to the structure they can recognize, are Toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors and nucleotide-binding oligomerization domain-like receptors. The cells expressing PRR can recognize conserved structures. For instance, miRNAs controls multiple immune processes such as regulating the innate immune responses of macrophages, dendritic cells and NK cells; involving in T-cell differentiation and function. Furthermore defective PRR function might lead to autoimmune or auto-inflammatory diseases, since nucleic acids (DNA and RNA) is commonly shared by the pathogen and host. Additionally, damage associated molecular patterns (DAMP), pathogen associated molecular patterns (PAMP), microbiome associated molecular patterns are the subtypes of PRR[6,7].

Mononuclear phagocyte system (MPS) composed by monocytes, macrophages, and DCs that have phenotypical and functional overlaping boundaries leading to uncertainty in differentiating them form each other. Antigen-presenting cells (APCs) express PRR and characterized by their ability to recognize, process and present antigens for activation of innate and adaptive immunity. The classical APCs include DC, monocytes and macrophages, although parenchymal cells can also act as APCs. MPS may be precursor of some APCs of liver, namely DCs and Kuppfer cells (KCs)[8].

ILCs are a recently identified family of heterogeneous variety of T cells and non-T cells, including NK cells, CD56+ Tcells, natural killer T cells (NKT), gamma/deltaT cells, mucosal- associated invariant T cells, lymphoid tissue-inducer cells and cells that produce IL-5, IL-13, IL-17 and IL-22. ILCs not only regulate innate and adaptive immune responses by promoting DC maturation into APCs, they have function in lymphoid tissue formation and the homeostasis of tissue stromal cells remodeling the tissues[9,10].

Adaptive IS

The adaptive immunity evolutionarily developed later than innate immunity in high-class vertebrates. The adaptive immune response occurs as second phase of immune response, mediated mainly by lymphocytes, and characterized by the features of antigen-specific response and memory response. It is initiated by antigen presentation lymphocytes. The main lymphoid repertoire includes T-cells, B cells. B cells produce specific antibodies in response to a specific antigen. These antibodies are crucial for T cells activation against bacterial infections and development of active immunization after vaccination[7,11]. However, the major mediator of adaptive immune response is the T cells, which control both the establishment and regulation of adaptive immunity.

T cells are identified by CD3 and T cell receptors (TCRs) positivity, and have vital importance in the adaptive and innate immunity. Conventional T cells express alpha-beta type TCR. Gamma-delta T cells are located in skin, genitourinary tract mucosa and gut, as well as liver. The naive T cells produced in bone barrow migrates to thymus and differentiate into 2 main subtypes are Th (helper) and Ts (supressor). The differentiated T cells are exported to periphery, where they become effector T cells upon activation by APCs or B cells. T cell activation requires binding of TCR to major histocompatibility complex (MHC), as well as binding of co-stimulatory molecule present on T cells to its co-receptor on APCs (*e.g*., binding of CD28 to B7). Th cells express CD4, which recognizes antigens in the context of MHC class Ⅱ, and are mainly regulatory cells. Ts are cytotoxic cells carrying CD8 receptors, which are activated by MHC class I molecules[11]. Recently, CD4+ cells have been divided into subsets according to their distinct cytokine production and function; Th1, Th2, T17, Treg, Tfh (follicular T helper). Some features of CD4+ cells are as shown on Table 1. Treg cells express CD4+CD25+ and are essential for maintaining immune homeostasis and self-tolerance. Treg cells either naturally produced from CD4+ thymocytes in the thymus or iTreg cells are induced at periphery from naive CD4+ T cells in response to the low-dose stimulation of TCR, TGF-beta and IL-2. Beside all these effector T cells, there are also memory T cells. Id3 is the key transcriptional regulator for controlling T-cell differentiation into either effector T cells or memory T cells by its action though mTORC signaling[7,9,12].

DCs are professional APC, which can recognize foreign antigens by their PRR, initiate immune response and constitute a bridge between innate and adaptive immunity. They primary screen surrounding microenvironment by antigen sampling and direct IS towards pro- or anti-inflammatory response[6]. DCs are found throughout the body as immature DCs and subdivided as plasmacytoid (or lymphoid) DCs and myeloid DCs. Plasmacytoid DCs mediate anti-viral immunity by its capability of viral recognition and type 1 interferons secretion. The myeloid DCs constitute conventional MPS derived DCs in blood, interstitial DCs in tissues, Langerhan cells in skin and monocyte-derived DCs. mDC can internalise antigens by phagocytosis, pinocytosis or receptor-mediated endocytosis. After generation of peptide by proteolytic degradation within endocytic vesicles, it complexes with newly synthesized MHC class Ⅱ molecule within endocytic compartment, and then is carried *via* the trans-Golgi network to the cell surface. The recognition and internalization of pathogens by DCs leads to maturation of them into professional APCs, which have altered adhesion molecule and chemokine receptor expression.

Table 1 Features of CD4+ cell subsets

	Th1	Th2	T17	Treg	Tfh
Produced Cytokines	IFN-gama, TNF-alpha, IL-2	IL-4, IL-5, IL-9, IL-10, IL-13	IL-17A, IL-17F, IL-21, IL-22, IL-26	TGF-beta, IL-10	CXCR5, IL-21
Immune response mediated aginst	Intracellular pathogens	Extracellular parasites, allergy, humoral response	Extracellular bacteria and fungi, autoimmunity	IgA secretion, self-tolerance	Differentiation of B cells
Master transcription factors for differentiation	T-bet	GATA-3	RORct	Foxp3	Bcl6
Effected cells	Macrophages, cytotoxic cells activated	Eosinophils, mast cells activated	Neutrophils activated	B cells activated Th1, Th2, Th17 supressed	B cells activated

IFN: Interferons; IL: Interleukin; TGF: transforming growth factor; TNF: Tumor necrosis factor.

After maturation DCs leave primary side of infection through lymphatic's to carry the internalized pathogen to secondary lymphoid organ. The professional APCs can be either immunogenic DCs which express high levels of MHC and co-stimulatory molecules, and secrete IL-12, IL-18, IL-21 and IL-23 or tolerogenic DCs having low expression levels, express inhibitory receptors, such as programmed death ligand-1, and releasing suppressive cytokines, such as IL-10, IL-27 and TGF-beta. Immunogenic DCs stimulate naïve CD4+ T cells to differentiation into effector cell mediating adaptive immunity against specific pathogen. On the other hand, if the antigenic peptid is presented to naïve CD4+ T cell by tolerogenic DCs, immune tolerance develops either at thymus or periphery. The consequen result in thymus is either T cell apoptosis or T cell maturation into natural Treg cells. The mechanisms for peripheral immune tolerance are anergy of T cells and exhaustion of T cells. The anergy arises when T cells are inactivated due to lack of co-stimulation. The exhaustion of T cells is characterized by expression of inhibitory receptors, namely programmed death-1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTLA4) and T cell immunoglobulin mucin-3. Interestingly in mice and humans, the lipid content of DCs in liver determines the maturation type of APCs, as lipid content decreases tolerant immune response is favoured. This phenomenon might be important for progression of simple steatosis into steatohepatitis. The relationship of autoimmune diseases with infection and environmental pollution and is very well known fact. It is though that the similarity between insulting antigen and self antigens of individuals with susceptible HLA haplotypes causes a shift during APCs maturation from tolerogenic DCs towards to immunogenic DCs, leading to differention of naive T cells into effector ratherden tolerogenic cells, and ending in loss of self-immune tolerance[1,9,11].

NK express CD56 in the absence of CD3, but NKT express both of them. NKT mediate anti-tumor effect by activating CD8+ T cells cytotoxicity or overriding the tolerogenic mechanisms through counter-regulation of Treg cells. NKT can identify glycolipid antigens and subtyped into two according to TCR expression profile. Type 1 or invariant NKT (iNKT) carry an invariant TCR alfa-chain pairing with a limited number of beta-chains, whereas type 2 NKT cells express a diverse array of TCRs that recognize CD1d which is MHC class I-like molecule. Innate T lymphocytes (ITLs) is composed of iNKT cells and gamma-delta T cells. ITLs regulate adaptive immune response through its key roles in initiation and polaration of APCs and other cells of IS. This feature of ITLs has made them target as immunomodulation for treatment of autoimmune diseases[1,9].

LIVER AS AN ORGAN OF IS

In order to keep homeostasis for survival, the immune response had to continuously adopt according to age, sex, dietary antigens, hormones (*i.e.*, pregnancy and lactation), and external stress factors such as microbiota, environmental flora or exposed chemicals[13]. Therefore IS has a dynamic nature and has a wide "range of normal". Beyond being a metabolic organ attached to gut, liver recently has been defined as central axis in IS controlling local and systemic immune reactions and tolerance. All types of liver cells have active immune function, including both parenchymal cells (hepatocytes, cholangiocytes) and non-parenchymal cells [liver sinusoidal endothelial cells (LSECs), hepatic satellite cells (HSCs) or ito cells, KCs, neutrophiles, mononuclear cells, lymphocytes (B cells, T cells, NK cells, NKT cells, ITL)]. Parenchymal cells occupy most of liver volume (78%-80%). Non-parenchymal cells and extracellular space represent the remaining 5%-6% and 14%-17%, respectively[11,14].

The unique anatomical and histological features of liver are important for its immune functions. The liver is located at the junction between systemic and portal circulation. It is supplied by approximately 1.5 L of blood every minute; 2/3 *via* the portal vein and 1/3 *via* the hepatic artery. The double blood supply carries a massive antigenic load from the gastrointestinal tract and systemic circulation to liver. The blood, coming from these two sources mixes within sinusoids, and then flows through hepatic lobule from peri-portal area towards central vein. The fenestrated structures of sinusoids enable intimate interaction of antigens and blood immune cells with hepatocytes, KCs and HSCs at space of Disse. The abundant cells of the innate and adaptive ISs are located in hepatic sinusoids, and have ability for pathogen sensing, phagocytosis, cytotoxicity, cytokine release and antigen presentation to T cells.

The antigen-rich blood passing through the liver sinusoids is "scanned" by IS, which is tightly regulated between activation and tolerance. The liver remains tolerant to harmless dietary antigens, products of commensal gut microbiota and auto-antigens, while responds to exogen toxins, a variety of blood-borne or gut originated viruses, bacteria and parasites, as well as to metastatic cells, which try to home to the liver. Therefore, immune roles of liver can be divided into 2 groups; immune surveillance and induction of peripheral immune tolerance[3,15]. Indeed, the hepatic IS plays predominantly tolerogenic role. This can clinically be observed in liver transplant patients, *e.g.*, liver allograft from major MHC or even ABO mismatched donors can be transplanted; if combined transplantation is done with organs from the same donor, non-liver allografts are more likely to be accepted; "operational tolerance", which describes a patient with clinically normal graft function without needing immunosuppression, developments in up to 50% of hepatic transplantations[16].

Immune surveillance function of liver

The liver relies on its strong immunity for its immediate and efficiend defense against potentially toxic agents without triggering harmful immune response towards self-structures. Liver, primarily hepatocytes, synthesizes the major amount of proteins involved in local and systemic immune responses. These proteins are called acute phase reactants such as fibrinogen, proteinase inhibitors, complement proteins, PRRs [*e.g.*, C reactive protein, lipopolysaccharide (LPS)-binding protein, peptidoglycan-recognition protein, soluble CD14], opsonizing proteins (*e.g.*, mannose-binding lectin, serum amyloids), cytokines [*e.g.*, IL-6, tumor necrosis factor-alpha (TNF-alpha) and transforming growth factor-beta (TGF-beta)], and hepcidin. The acute phase reactants function during innate immune response, mediate inflammation as well as tissue repair and regeneration. Their expression in hepatocytes is controlled by liver-enriched transcription factors (*e.g.*, HNFs, C/EBPs), pro-inflammatory cytokines (*e.g.*, IL-6, IL-22, IL-1β, TNF-α), and downstream signaling pathways (*e.g.*, STAT3, NF-kappa B)[7,15].

Neutrophils are short-lived, circulating, phagocytic cells, which are recruited to site of infection by cytokines and chemokines, mainly IL-1 and IL-8. They are the first responders to infections and act by three main mechanisms; phagocytosis (requiring opsonization), generation of reactive oxygen species and degranulation (releasing enzymes and antimicrobial peptides), and formation of neutrophil extracellular traps (NETs). NETs are another mechanism of microbe killing. Nuclear DNA ligated with various microbicidal proteins released by activated neutrophils forms these webs. Under normal conditions the liver have few neutrophils, but they rapidly accumulate following necrosis. Neutrophils can rapidly shift their adhesive mechanisms in order to reqrude and form NETs in liver as a response to both endotoxin and bacteria[14].

Macrophages have been classified as classically activated macrophages (M1, secretes TNF-α, IL-1, IL-6, IL-8 and IL-12) or alternatively activated macrophages (M2, secretes IL-10 and TGF-β) based on their cytokine secretory patterns and proinflammatory *vs* immunoregulatory activity which however, are interchangeable functional states depending on the microenvironment the macrophages encounter[6,11]. KCs are fixed macrophages specialized at eliminating insoluble waste by phagocytosis and capable of processing and presenting antigens to T cells and participate in the regulation of the adaptive immune response. KCs reside on intravascular side of LSECs, and capture bacteria and able to bind component 3b under shear conditions while flowing through sinusoids. The role of KCs in microbial killing depends on the nature of the pathogen and on the recruited immune cells to the inflammation side. The characteristic feature of PRRs expression in liver is their constitutive expression and continuous low-level stimulation by endotoxins from gut. TLR4 is an PRRS expressed on all liver cells and it binds and clears endotoxins, and so initiates secretion of pro-inflammatory and anti-inflammatory cytokines[7].

Although, more than 80% of the CD3+ T cells are alpha-betaT-cells, the liver is also enrichmented by NKs and unconventional lymphocytes (NKT and gamma-delta T cells). The gamma-deltaT cells is 5 times higher in the liver (15%) then the periphery[4].

Hepatocytes, which constitutively express intercellular adhesion molecule-1, can directly interact with T cells through the fenestrations of LSECs. IFN-gamma primes hepatocytes to APCs by dose dependently enhancing HLA expression; from moderate HLA class I expression to enhanced HLA class Ⅱ expression at low to high IFN-gamma levels. Hepatocyte primed naïve T cells either become effector T cells or undergoes apoptosis in the absence of co-stimulatory signals. On the other hand, cholangiocytes are relatively spared form antigenic stimulation from blood, but not from those one secreted into bile. Cholangiocytes can express TLRs, HLA class I at a low frequency and co-stimulatory molecules. Hepatotropic viruses (*i.e.*, CMV) enhances HLA class I expression without inducing HLA class Ⅱ. In pathological conditions such as that of PBC, cholangiocytes act as APC by overexpress HLA class Ⅱ, as well as CD80 and CD86 co-stimulatory molecules. The limited experimental data supports that HSCs have capacity to act as APCs. The presentation of lipids to T-cells and NKT cells by HSCs can cause activation or tolerance in IS depending on co-stimulation[4,7].

Liver mediated peripheral immune tolerance

Besides conferring strong local innate immunity, the liver regulates immune homeostasis as being a major site for induction of T cell mediated local and systemic adaptive immune response. Both resident and transiting T and B cells scattered throughout the parenchyma and the portal tracts become important effector cells of defensive adaptive immune in liver after activation by APCs. Both hepatic parenchymal and non-parenchymal cells can act as APCs depending on the stimulus and special cytokine milieu. The classical hepatic APCs are

DCs and reticulo-endothelial system (including KCs and LSECs). However, hepatocytes and cholangiocytes become non-conventional APCs by expressing MHC Ⅱ, if there is under pathological insult or persistent inflammation. Classical hepatic APCs constitutively express MHC class Ⅰ-Ⅱ, co-stimulatory receptors and molecules that promote antigen uptake (*e.g.*, mannose and scavenger receptors). Under the physiological liver conditions, DCs are at immature developmental status and there is high production an anti-inflammatory cytokine (IL-10, TGF-b, TNF-a and prostaglandins) from reticulo-endothelial cells. This reduces capacity of APCs to activate effector T cells and lead to generation of anergic T cells and Treg cells. In other words, the tolerogenic nature of the liver by preferentially suppressing adaptive immunity is created by APCs, which kill or suppress effector CD4+ and CD8+ T cells and induce maturation of naïve T cells into Treg cells. Since diversion of portal flow results in the loss of immune-tolerance, it is hypothesized that physiological concentration of endotoxin is essential for maintain hepatic immune tolerance. LPS from gut microbiota drained to the liver by portal vein, modulates LSECs mediated CD4+ T cell activation by inducing secretion of IL-10 from LSECs and by down-regulating expression of MHC class Ⅱ, CD80 and CD86 on LSEC. Another proposed mechanism for hepatic induction of peripheral immune-tolerance is clonal deletion/apoptosis of antigen-specific T cell at liver. HSCs may have a role in creation of tolerogenic micro-environment. HSCs have a capacity to serve as APCs, expand Treg cells, and promote T cell apoptosis (*via* B7-H1, PDL-1) or inhibit cytotoxic CD8+ T cells[4,9,15].

The local and systemic self-tolerance can be overridden and so autoimmune diseases can be initiated by several pathological immune mechanisms developed in liver. First of all, pathological antigen presentation might generate of auto reactive T cells and B cells due to defective clonal deletion (apoptosis of antigen-specific T cells). Similarly ILCs also switch on the autoimmunity by promoting antigen presentation with classical APCs, by releasing cytokines that polarize immune response towards effector T cells. ILCs may also be important mediators autoimmune liver injury by killing hepatocytes and/or bile duct epithelial cells. Pathological endotoxemia caused by dysbiotic microbiota may switch immune response from Th2 to Th1 predominance. Treg cells regulate both innate and adaptive immunity through regulation of CD4+ cells, KCs and LSECs. Therefore, defective function of Treg cells impairs hepatic immune tolerance leading to autoimmune hepatitis[4,7].

SPECTRUM OF IMMUNE HOMEOSTASIS IN LIVER

Hepatic IS is always active, regardless the overall response outcome. The nature of insult to liver and spectrum of activated cells determines the clinical picture. Healthy individuals have balanced immune surveillance of pathogens together with immune tolerance towards self-antigens. The over immune tolerance in liver leads to chronic infections with viruses or hepatic metastasis of cancer cells. In contrast the over activation of hepatic immune response causes fulminant hepatitis, allograft rejection or autoimmune diseases.

Hepatic immune hemoastasis is continuously re-balanced during clinical courses of cirrhosis. Patients with compensated cirrhosis have hyperactivated IS depending on underlying etiology of the liver diseases. Hepatic decompensation is associated with increased intestinal permeability. The episodic translocation of gut microbiota and their endotoxins into portal circulation triggers systemic and hepatic inflammation. PAMRs recognizing LPS, lipopeptides, glycopolymers, flagellin and bacterial DNA/RNA, activate innate and adaptive immunity. The released pro-inflammatory cytokines and chemokines cause hepatic injury and activation of DAMP. The viscous cycle between members of PRR, namely PAMP and DAMP exhausts IS and so, switches immune response from a predominantly "pro-inflammatory" to wards "immunodeficient" status. This very late stage of cirrhosis is clinically defined as acute- on-chronic liver failure (ACLF). The immune deficient state in ACLF patients is called cirrhosis associated immune deficiency[15].

HERBAL TREATMENTS WITH POTENTIAL THERAPEUTIC EFFECT ON LIVER

Herbal treatments are very often multifaceted blends of slightly processed medicinal plants, parts of the plants or products of the medicinal plants, which are traditionally accepted, comparatively low side-effects, and naturally compatible with the human body. Herbal remedies are applied for the treatment of a variety of indications and disorders, including hepatic as well as immunological problems (Table 2). Since scientific studies on herbal treatments have shown that they might effect cytokine and immunoglobulin secretion, cellular co-receptor expression, histamine release, lymphocyte proliferation, and cytotoxic activity, thus, herbal preparations might modify immune functions. In this study, literature was surveyed based *on in vitro*, *in vivo* and clinical studies on hepatoprotective, as well as immunostimulant and/or immunomodulator effective medicinal plants, which are lead by ethnopharmacological data. Table 2 was established, which covers common name, scientific name, effective part, known phytochemical content of the plant, ethnopharmacological/clinical effects, and medicinal preparation with their corresponding references. Due to complexity of the herbal treatments, the complete scientific data on mechanism of action is lacking, although clinical outcomes of herbal treatment are promising and leading the researchers to take on demanding scientific studies on the immune activity of herbal remedies (Table 3). The most applied medical plants in herbal treatments were selected and their mechanism of action on liver diseases and on immun system were searched to establish the Table 3. Flavonoid

Table 2 Plants are effective on liver disorders and immune system

Common name	Scientific name	Effective part	Phytochemical content	Preparation on liver disorders[1]	Ref.
Chaff-flower	*Achyranthes aspera* L.	Whole plant	Ecdysterone, achyranthine, betaine, pentatriaontane, 6-pentatriacontanone, hexatriacontane and tritriacontane	Natrossil natiris	[28-30]
Fennel	*Foeniculum vulgare* Mill.	Root	Coumarins (bergapten, isopimpinellin, anthotoxin), flavonoids (quercetin, rutin)	Presselin dyspeptikum presselin, bupleurum compound phytomedicine, epagest lampugnani	[18,25,31]
Korean Ginseng, Chinese Red Ginseng	*Panax ginseng* Mey.	Root	Polysaccharides, saponins, ginsenoside	Tripid teguhsindo	[32-34]
Yarrow	*Achillea* sp.	Flower	Volatile oils, flavonoids, terpenoids, alkaloids, saponins, sesquiterpenlactones	Liv-52 drops, cheiranthol klein	[35-38]
Carqueja	*Baccharis trimera* (Less) DC	Epigeous part	Flavonoids, diterpenoids	Boldina Plata	[39-41]
Chicory	*Cichorium intybus* L.	Aerial part, root, leaf	Saccharides, methoxycoumarin cichorine, flavonoids, essential oils, anthocyanins	Natusor hepavesical soria natural, Liv-52 drops	[42-46]
Globe artichoke	*Cynara cardunculus var. scolymus* L.	Leaf	Sesquiterpenes lactones (cynaropicrin), flavonoids (cynaropicrin), phenolic acids (mainly caffeic acid derivatives)	Livstim mediherb, livton complex mediherb, lorbihepatic bioquimico, olocynan makros, rapacholin C herbapol wroclaw, farmasa, sylicynar herbapol poznan, alcafelol luper, bagohepat bago, armstrong, benevolus schwabe, boldina plata, cinarepa cristalfarma, colachofra EMS, cynarex roux-ocefa, herbapol wroclaw, cynarzym N altana, digestron loprofar, epagest lampugnani, figatil catarinense, salus, hecrosine B12 ortoquimica, hepatofalk falk, jurubileno ibefar	[47,48]
Pale purple coneflower	*Echinacea pallida* (Nutt.) Nutt. *Echinacea angustifolia* (DC.) Hell. *Echinacea purpurea* (L.) Moench	Whole plant	Alkamides, polysaccharides, glycoproteins, cichoric acid (a derivate of caffeic acid)	Andrographis complex mediherb, kalbe, hepatin lapi, imudator pyridam, herbal cleanse vitaplex	[49-52]
Faise daisy	*Eclipta alba* (syn *E. prostrata* L.)	Aerial part	Tannins, flavonoids, coumestans, saponins, alkaloids	Dipana promed	[53,54]
Chamomile	*Matricaria chamomilla* L.	Flower	Coumarin (herniarin and umbelliferone), phenylpropanoids (chlorogenic acid and caffeic acid), flavonoids (apigenin, apigenin-7-o-glucoside, luteolin, luteolin-7-o-glucoside, quercetin, rutin, naringenin), blue essential oils	Presselin dyspeptikum presselin, cholesol herbapol wroclaw, gotas digestivas bunker	[42,55-57]
Milk thisle	*Silybum marianum* (L.) Gaertn.	Seed	Polyphenolic flavonoids(silymarin, isosilyins, silibinins, silydianin silychristin)	Liverine cardinal, livermin korean ginseng, liverton siffra, livosil-b centaur, livstim mediherb, livton complex mediherb, lomacholan lomapharm, phytohepar steigerwald, poikicholan lomapharm, prol procare, samarin berlin pharm, schwohepan S schworer, silegon teva, silibene merckle, silicur hexal, silimalon nikkho, silimarin benedetti, silimarit bionorica, silimax filofarm, silirex lampugnani, siliver farmasa, silliver abbott, silmar hennig, silvaysan sanum-kehlbeck, silybon micro, silygal ivax, silyhexal hexal, sily-sabona sabona, mepha, sivylar ranbaxy, sylicaps herbapol lublin, sylicynar herbapol poznan, sylimarol herbapol pruszkow	[18,19,58,59]

				Syliverin aflofarm, sylivit herbapol poznan, solas, vionin nf tempo scan pacific, alepa duopharm, apihepar madaus, *vıa* tris, aptivium liver support cynergen, ardeyhepan emonta, ardeypharm, bibol leloup hexa, bilisan duo repha Bioglan liver-vite bioglan, bupleurum complex mediherb, bupleurum compound phytomedicine, carsil sopharma, cefasliymarin cefak, cheiranthol klein, soho capsule/syrup, depatox progen, durasilymarin merck dura, eleparon sankyo, epagest lampugnani, flavobion zentiva, hegrimarin strathmann, strathmann, hepabene ratiopharm, merckle, ratiopharm, hepabesch strathmann, hepadigenor baliarda, hepaduran v otw, loges Capsule, hepamax dankos, hepa-merz sil merz, hepar-pasc pascoe, heparsyx n syxyl, heparviton bode, tempo scan pacific, hepatin lapi, kalbe, falk, darya-varia, hepatos, Yung shin, heplant spitzner, herbal liver formula faulding, worwag, legalon-madaus, laragon roemmers, ıfet, leveron vesco, limarin serum ınstitute, herbal cleanse vitaplex	
Dandelion	*Taraxacum officinale* G.	Root	Sesquiterpenes, saponins, phenolic compounds, flavonoids, sugars	Naturica DFM ıkapharmindo, livstim mediherb, livton complex mediherb, berberis complex blackmores, cholesol herbapol wroclaw, cinarepa cristalfarma, hepatofalk falk, herbal cleanse vitaplex	[60-63]
Radish	*Raphanus sativus* L.	Leaf, root	Flavanoids, terpenoids, alkaloids, saponins, sterols	Rapacholin AC herbapol wroclaw, rapacholin c herbapol wroclaw	[64-67]
Caper	*Capparis spinosa* L.	Root bark	Sugars (glucose, arabinose, mannose, galactose), lipid, volatile oils	Liv-52 drops	[68-71]
Kinkéliba	*Combretum micranthum* G. Don	Leaf	catechins, glycosylflavones, flavans, galloylated c-glycosylflavone derivatives, flavan-piperidine alkaloid	Tisane mediflor N°5 hepatique	[72-74]
Arjuna	*Terminalia arjuna* (Roxb.) Wight and Arn.	Bark	Arjunolic acid, tomentosic acid, arjunin, *β*-sitosterol, ellagic acid, leucodelphinidin, tannins	Liv-52 drops	[75-77]
Coffee senna	*Cassia occidentalis* L.(*Senna occidentalis)*	Leaf	Anthraquinones, saponins, sterols, triterpenes, quinines, tannins, flavonoids	Tisane mediflor N°5 hepatıque, Liv-52 drops	[78-80]
Liquorice, Licorice	*Glycyrrhiza glabra* L.	Root	Triterpene saponins, flavonoids, isoflavonoids and chalcones, glycyrrhizic acid	Tisane mediflor N°5 hepatıque, neo-minophagen C dexa, torii, curliv soho, soho capsule/syrup	[18,26,81]
Holy basil	*Ocimum sanctum* Linn.	Leaf	Volatile oils (eugenol, euginal, urosolic acid, carvacrol, linalool, limatrol, caryophyllene, methyl carvicol), anthocyans, alkaloids, flavonoids, tannins, carbohydrates,xylose, polysaccharides	Andrographis complex mediherb	[22,82-85]
Rosemary	*Rosmarinus officinalis* L.	Leaf	Diterpenoids, triterpenoids, phenolic acids, and flavonoids, carnosic acid, carnosol, rosmarinic acid	Tisane mediflor N°5 hepatıque, natusor hepavesical soria natural, cinarepa cristalfarma	[86-88]
Red sage, Danshen	*Salvia miltiorrhiza* Bunge.	Root	Tanshinones (tanshinone ı, tanshinoneıı, cryptotanshinone) miltirone and salvianolic acid a, b	Bupleurum complex mediherb	[18,89,90]
Common mallow	*Malva sylvestris* L.	Leaf	Amino acids/protein derivatives, flavonoids, mucilages, terpenoids, phenol derivatives, coumarin	Tisane mediflor N°5 hepatıque	[91-93]
Tinospora, Guduchi, Giloya	*Tinospora cordifolia* (Willd.) Hook. f. and Thoms. (Guduchi)	Root, stem	Flavonoids, alkaloids, sesquiterpenes, diterpenes arabinogalactan, syringine, cordiol, cordioside, cordifoliosides (a and b), berberine, tinosporine, giloin, giloinin	Dipana promed	[22,33,94-96]

Boldo, Boldu, Boldus	*Peumus boldus* Molina	Leaf	Alkaloids (isoquinoline-boldine, isoboldine, 6a,7-dehydroboldine, isocorydine, isocorydine-n-oxide, norisocorydine, laurolitsine, laurotetanine, n-methyllaurotetanine, reticuline, (-)-pronuciferine, sinoacutine), flavonoids, volatile oil, coumarin, resin, tannin)	Tisane mediflor N°5 hepatıque, natrossil natiris, natusor hepavesical soria natural, prinachol zurita, farmasa, alcafelol luper, berberis complex blackmores, boldina plata, boldopeptan neo quimica, colachofra ems, cynarzym N altana, eparema nycomed, figatil catarinense, gotas digestivas bunker, jurubileno ıbefar	[97-99]
Greater celandine	*Chelidonium majus* L.	Aerial parts	Isoquinoline alkaloids, such as sanguinarine, chelidonine, chelerythrine, berberine and coptisine, (-)-turkiyenine)	Livstim mediherb, livton complex mediherb, natusor hepavesical soria natural, schwohepan S schworer, berberis complex blackmores, chelicur hasco-lek, cynarzym N altana, hepatofalk falk, falk, darya-varia	[100-105]
Gale of the wind	*Phyllanthus niruri* L.	Whole plant	Flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins	Natrossil natiris, meprofarm, dipana promed, gramuno graha, hepimun landson, ımudator pyridam	[106-108]
Kutki	*Picrorhiza kurroa* Royle ex Benth.	Rhizome, root	Iridoid glycoside (picrovil)	Dipana promed	[109,110]
Rhubarb	*Rheum emodi*	Rhizome	Anthraquinone (rhein, chrysophanol, aloe-emodin, emodin, physcion, and their glycosides) and stilbene (picetannol, resveratrol and their glycosides), flavonoids, glycosides, tannins, volatile oils, saponins	Natrossil natiris, boldopeptan neo quimica, eparema nycomed, SIT, hepatofalk falk	[111]
Magnolia-vine, Schisandra	*Schisandra chinensis* (Turcz.) Baill.	Fruit	Dibenzocyclooctadiene derivative lignans (or schisandra lignans), organic acids (citric, malic, fumaric and tartaric acid), sugars, vitamic C, vitamin E, phenolic acids, tannins, phytosterols, essential oil	Curliv soho, soho capsule/syrup, hepacell medikon, hepamax dankos	[31,112,113]
European black nightshade	*Solanum nigrum* L.	Whole plant	Glycoalkaloids, glycoproteins, polysaccharides, polyphenolic compounds (gallic acid, catechin, protocatechuic acid (pca), caffeic acid, epicatechin, rutin, naringenin)	Liv-52 drops, dipana promed	[114-117]
French tamaris	*Tamarix gallica* L.	Aerial parts	Tannin, tamarixin, tamauxetin, troupin, 4-methylcoumarin and 3,3′-di-o-methylellagic acid, tannic acid, 4-methylcoumarin and 3,3′-di-o-methylellagic acid	Liv-52 drops	[118,119]
Turmeric	*Curcuma longa* L.	Rhizome	Curcuminoid	Meprofarm, tripid teguhsindo, turmerik knop, aptivium liver support cynergen, chelicur hasco-lek, galena, ıvax, cinarepa cristalfarma, depatox progen, heparviton bode, tempo scan pacific, kalbe, hepatin lapi, falk	[22,31,120]
Ginger	*Zingiber officinale* Roscoe	Rhizome	Volatile oils, pungent phenol compounds [sesquiterpenoids,beta-sitosterol palmitate, isovanillin, glycol monopalmitate, hexacosanoic acid 2,3-dihydroxypropyl ester, maleimide-5-oxime, p-hydroxybenzaldehyde adenine, 6-gingerol, 6-shogaol, 1-(omega-ferulyloxyceratyl) glycerols]	Presselin dyspeptikum presselin, dipana promed, herbal cleanse vitaplex	[121-127]

[1]Martindale W, Sweetman SC. Martindale: The complete drug reference. Pharmaceutical press, 2007.

derivatives such as silybin, silymarin, obtained from milk-thistle [*Silybum marianum* (L.) Gaertn.] decreased alkaline phosphatase (completely) and gamma-glutamyl transpeptidase (partially) in CCl_4 induced liver damage[17]. Moreover, it has been claimed that Silymarine containing preparations are the principal therapeutic of choice in liver diseases caused by oxidative stress. Many studies have proven that plant phyto compound Silymarin has medical applications to cure (alcoholic and non-alcoholic) fatty liver, cirrhosis, ischaemic injury, drug and chemically-induced hepatic toxicity, radiation toxicity, viral and toxic hepatitis by means of its anti-oxidative, anti-lipidperoxidative, anti-fibrotic, anti-inflammatory, liver regenerating and immunomodulating effects. Several studies have identified that continuous usage of Silymarin has significantly proved to increase the survival period of patients with alcohol-caused liver cirrhosis and primary liver cancer[18] (Figure 1). Scientific studies also

Table 3 Commonly used plants on liver disorders and their effect mechanisms

Scientific name	Effect/mechanism on liver	Effect/mechanism on immun system	Ref.
Curcuma longa L.	Acute liver damage by chemicals, *e.g.*, ethanol, CCl_4, Dimethylnitrosamines	Immunostimulant, immunomodulatory The extract of the rhizome *C. longa* increased both Th1 (IL-2 and IFN gamma) and Th2 (IL-10) cytokines indicating its dual immune functions. NR-INF-02 significantly increased the IL-2 and IFN gamma levels in Con A stimulated splenic lymphocytes. The above results indicated that NR-INF-02 showed a specific immunity response by stimulating both Th1 and Th2 cells Polysaccharide fraction of the rhizome showed potent immunostimulatory activity towards proliferation of splenocytes cell number and IL-10 secretion. Polysaccharides might be contributing to this proliferative and cytokine release property in murine splenocytes Hot water extracts of the rhizome showed that the high polarity fraction exhibited stimulatory effects on PBMC. The cytokine productions (TGF-beta, TNF-alpha, GM-CSF, IL-1alpha, IL-5, IL-6, IL-8, IL-10, IL-13, *etc.*) have been modulated by a polysaccharide-enriched fraction.The proportion of CD14 positive stained PBMC was increased by the fraction Anti-HIV-1 and HIV-2	[18,22-24]
Foeniculum vulgare Mill.	Oxidative stress of the liver bacterial and viral infections anti-inflammatory, acute hepatotoxicity	Immunomodulatory Antimicrobial, antifungal	[18,25]
Glycyrrhiza glabra L.	Cirrhosis fibrosis chronic viral hepatitis B and C	Immunomodulatory Leukocyte count and phagocytic index (carbon clearance) was increased significantly with the treatment of water extract of *G. glabra* root. Zinc (45 mg/kg) in combination with ALE (0.75 g/kg) showed highly significant increase of leukocyte count and phagocytic index	[18,26,27]
Silybum marianum (L.) Gaertn.	Oxidative stress inflammation and fibrosis alcohol-induced cirrhosis mushroom poisoning viral hepatitis	Immunomodulatory Flavonoids from *S. marianum* normalize immunoregulatory defects *via* restoration of the cellular thiol status. T-cell activation (CD69), along with a significant decrease in TNF	[18,19]

IFN: Interferons; TNF: Tumor necrosis factor; IL: Interleukin; TGF: transforming growth factor; HIV: Human immunodeficiency virus; PBMC: Peripheral blood mononuclear cells; GM-CSF: Granulocyte-macrophage colony-stimulating factor; ALE: Aqueous liquorice extract.

have shown that, both silybin and silymarin normalized immunoregulatory failures by restoration of the cellular thiol status, T-cell activation (CD69), together with a substantial decrease in TNF[18,19]. Effects of the selected herbal medicines on immune and liver were summarized in Figure 1. Another study demonstrated that an edible plant Artichoke (*Cynara scolymus* L.) prevented CCl_4 and oxidative stress-induced hepatotoxicity and it protected the liver[20]. Inulin, obtained from artichoke, stimulates components of the IS[21]. The extract of the rhizome Turmeric (*Curcuma longa* L.), which has hepatoprotective plant, amplified both Th1 (IL-2 and IFN gamma) and Th2 (IL-10) cytokines signifying its dual immune roles. Polysaccharide fraction of this rhizome showed potent immunostimulatory action in the direction of proliferation of splenocytes cell number and IL-10 secretion. Polysaccharides of the plant extract might be causative of these proliferative and cytokine release assets in murine splenocytes. In different studies have been shown that the cytokine productions (TGF-β, TNF-α, GM-CSF, IL-1α, IL-5, IL-6, IL-8, IL-10, IL-13, *etc.*) have been modulated by polysaccharide-enriched fractions[18,22-24]. Fennel (*Foeniculum vulgare* Mill.) and liquorice (*Glycyrrhiza glabra* L.) have also shown immunomodulatory and hepatoprotective effects[18,25-27].

Herbal drugs are composed of complex mixtures of phytochemicals, unlike conventional and plant originated single compound drugs, which are composed of known chemical constituents and are precisely quantified. For that reasons studying the clinical effects of individual chemical constituents separately will not be accurate, due to various reasons, such as the synergistic or inhibiting effects of phytochemicals on each other and neutralization of harmful chemicals in the mixture by other compounds, which provides a flawless combination for therapeutic purposes. Aspects such as, absorption, distribution intrinsic concentration and metabolism of the drug should be known precisely to determine the dosage, safety margin and length of treatment. Moreover, future research should include characterization of multifactorial mechanisms of action, elucidation of adverse effects and well-designed clinical trials in pediatrics and geriatrics as well.

CONCLUSION

Scientists as well as immunologists, who study herbal treatments in hepatic diseases most be ready to face challenges and opportunities. *In vivo* and clinical molecular researches on immunomodulatory, immunoenhancing, immunostimulant effects of herbal treatments will offer novel perceptions into IS and immunotherapy. Not only single plant extract, but the interactions of the ingredients in a given herbal treatment formula determines the final clinical picture by finely tuning the balance between therapeutic effect and hepatotoxicity. Feature studies

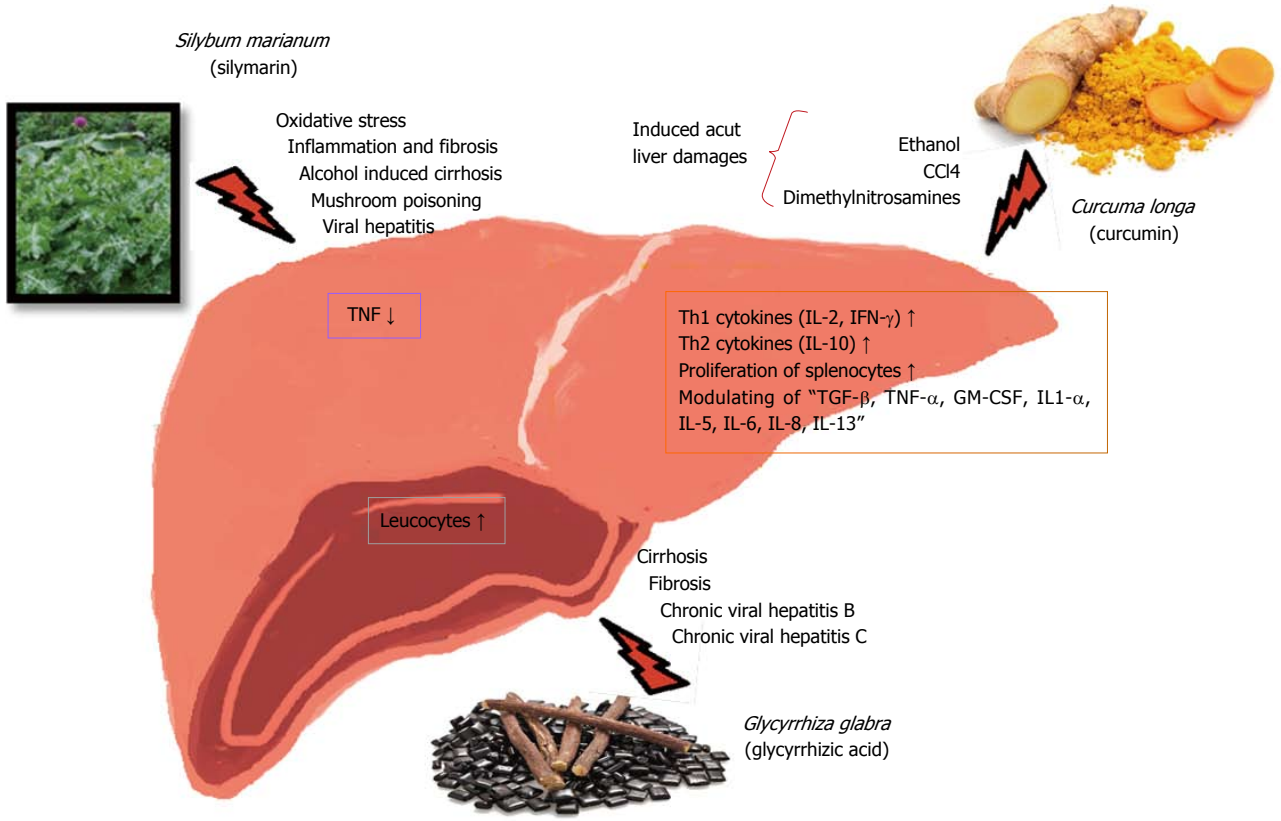

Figure 1 Immunological action mechanismes of some herbals on the liver. IFN: Interferons; TNF: Tumor necrosis factor; IL: Interleukin; TGF: Transforming growth factor.

must pricely define the interaction between the liver as an organ regulating local and systemic immune response and complex action mechanisms of herbal treatment.

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