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REVIEW OF HEPATOPROTECTIVE AGENTS IN HERBS

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Abstract

Hepatic disease is one of the main causes of death in the world and occurs commonly induced by alcohol, viral and drugs. Treatment of hepatic diseases by using synthetic drugs is lead to serious adverse effects. Due to that, herbal treatment has appeared as an alternative treatment with good value in treating hepatic diseases. Herbs have been used traditionally for treating hepatic diseases since the past centuries. Numerous phytochemicals from herbs have been found as hepatoprotective (ability to minimize the effect of hepatic diseases which eventually improve hepatic function) agents. Although there are reports from many researchers on the hepatoprotective agents in various herbs, these scientific data are scattered and no conclusive information especially for various induced hepatic diseases is achieved to date. The researchers just consider the phytochemicals in herbs with specific induced of hepatic diseases. This limits researches on mapping the hepatoprotective properties for various induced of hepatic diseases. Therefore, it is important to compile and study the hepatoprotective agents in herbs in order to provide a baseline for future research such as blending and new formulation of herbs. Phytochemicals such as silymarin, andrographolide, neoandrographolide, picroside, kutkoside, phyllanthin and glycyrrhizin and so on are known to act as hepatoprotective agents for treating hepatic diseases. This review focuses on the herbs and their mechanisms of phytochemical group as hepatopotective agents. It has been found that hepatoprotection agents generally exert multiple effects such as antioxidant, free radical scavenging, antiviral and anti-inflammatory properties. The vital mechanisms of hepatoprotection agents are probably due to the presence structure of flavonoids in herbal plants. The results of this study indicate that extracts of phytochemicals from certain herbs have good potentials for use in various induced of hepatic diseases.

Keywords: Hepatic diseases, Herbs, Alternative treatment, Hepatoprotective activity, Phytochemicals.

1. Introduction

Hepatic is a crucial and the major organ on human body that presents various interrelated functions. Hepatic disease is one of the main causes of death in the world [1-4]. The progress in the knowledge and management of hepatic disease have witnessed in the past 30 years. Modern treatment leads to serious adverse effects which eventually hepatic damage. Table 1 shows list of modern medicine have used in hepatic diseases with effect to human body. For example, corticosteroids and interferons performance in hepatic treatment are inconsistent, carry the risk of adverse effect and an expensive [3]. Besides that, lamivudine is used also to minimize the risk of chronic hepatitis B and cirrhosis. However, continuous use of lamivudine leads to appearance of a resistant hepatitis B virus mutant [5]. Hence, there is required for effective therapeutic agents with a low incidence of adverse effects. Herbs potentially constitute such characteristics [1].

Table 1. List of Modern Medicine in Hepatic Diseases with Effect to Human Body.

Modern Medicine	Specific hepatic diseases	Effect to human body	Ref.
Corticosteroids and interferons	-	Treatment inconsistent, carry the risk of adverse effect and an expensive	[3]
Lamivudine	Hepatitis B and cirhosis	Continuous use of lamivudine leads to emergence of a resistant hepatitis B virus mutant	[5]
Propylthiouracil	Alcoholic hepatic diseases	Render metabolically-compromised patients hypothyroid	[6]
Colchicine		No beneficial effect on either overall mortality or hepatic related mortality even though it has many potential therapeutic mechanisms of action including inhibition of collagen production, enhancement of collagenase activity and anti-inflammatory functions.	
Corticosteroids		Enhance the risk of infection and lack of applicability in many patients with alcoholic hepatitis.	
Pentoxifylline		Protective effects against hepatorenal syndrome and its excellent safety profile	
Ursodeoxycholic acid	Non-alcoholic fatty hepatic disease	Improves hepatic enzymes and hepatic histology in patients with various hepatobiliary diseases and improves oxidative stress.	[7]
Rosiglitazone	Non-alcoholic fatty hepatic disease	Increase risk of heart attack	[8]

The use of herbs in treating hepatic diseases has huge potential as alternative treatment. The easy convenience without the need for difficult pharmaceutical synthesis has increased awareness towards herbal medicines [1]. World Health Organization (WHO) has stated that the traditional medicine especially herbs as therapeutic practices have been emerged for hundreds of years, before the

development of modern medicine and are still in use today [4]. Herbal medicines are being applied about 80% of the world population mostly in the developing countries for primary health care [4, 9-10]. Numerous researchers [1, 3, 9-11] have been claimed that the large number of plants possess hepatoprotective activity including 170 phytochemicals isolated from 110 plants belonging to 55 families. Hepatoprotective herbal contains a variety of phytochemicals like flavanoids, phenols, coumarins, curcuminoids, lignans, essential oil and terpernoids [3]. The hepatoprotective activity in herbal plants is probably due to the presence of flavonoids [9]. Phytochemicals such as silymarin from *Silybum marianum*, andrographolide and neoandrographolide from *Andrographis paniculata*, picroside and kutkoside from *Picrorrhiza kurroa*, phyllanthin and glycyrrhizin from *Phyllanthus niruri*, glycyrrhizin from *Glycyrrhiza glabra* [1, 2] are known to act as hepatoprotective agent. These phytochemicals, which have proven as antioxidant, antiviral, antifibrotic or anticarcinogenic properties, can serve as primary compounds for further development as hepatoprotective drugs [1].

Adewusi and Afolayan reviewed the potential of natural product as hepatoprotective properties against various toxic chemicals that cause hepatic damage such as carbon tetrachloride (CCl_4), paracetamol, *D*-galactosamine, lipopolysaccharides, tuberculosis, dimethynitrosamine and petroleum ether. From this study, it is identified that glycosides, flavonoids, triterpenes and phenolic compounds as classes of phytochemicals with hepatoprotective activitiy [12]. While, Suruchi et al. compiled phytochemicals data from Indian medical plants that have been tested in hepatotoxicity models using modern scientific systems and also review the potential of phytochemicals in herbs that have hepatoprotective agents to treat inducing of hepatic diseases [9]. This review focuses on the herbs and their mechanisms of phytochemical group as hepatopotective agents which it should possess efficacy to treat inducing hepatic diseases caused by alcohol, viral and drugs. Due to that, this review is also aimed to compile data based on the hepatoprotective agents in herbs in order to provide a baseline for future research such as blending and new formulation of herbs to treat hepatic diseases.

2. Induction Factor of Hepatic Diseases

Generally, there are numerous causes that contribute to various hepatic diseases such as uncontrolled environmental pollution, drug abuse, poor sanitary conditions and expanding treatment with toxic drugs [1]. Commonly, some of the known category of hepatic diseases including viral hepatitis, alcohol hepatic disease, non-alcoholic fatty hepatic disease, autoimmune hepatic disease, metabolic hepatic disease, drug induced hepatic injury, gallstones and so on [13]. Acute hepatitis may be asymptomatic and usually can be resolved, but unresolved inflammation that continue for over than 6 months leads to chronic circumstance. Consequence of chronic hepatic disease, patient can develop portal hypertension and hepatic cirrhosis. Toxicity is the major cause of hepatic disease mainly occurs due to alcohol, viral and drugs [2].

The alcoholic hepatic diseases is differentiated by three key histological stages which is fatty hepatic (hepatic steatosis), acute alcoholic hepatitis and cirrhosis [14]. Long term alcohol consumption can effect in a variety of clinical syndromes and pathological changes ranging from fatty hepatic, fibrosis, cirrhosis and

hepatocellular carcinoma [14, 15]. Europe is the heaviest drinking region in the world in terms of the incidence of alcohol consumption, according to the WHO report 'European status report on Alcohol and Health 2010' and around 29 million human in the European Union still suffer from a chronic hepatic diseases [16].

The viral hepatitis is mostly responsible for both acute and chronic hepatic diseases. To date, hepatitis A, B, C, D, and E have been identified as causative in human. Hepatitis A is caused by infection with the hepatits A virus (HAV)-picornovirus due to consumption of contaminated food or water. While hepatitis B is caused by infection with the hepatitis B virus (HBV)-hepadnavirus and may lead to acute and chronic hepatic hepatitis. Hepatitis C may lead to chronic form of hepatitis culminating to cirrhosis and caused by infection with the hepatitis C virus (HCV). HCV is transmitted through percutaneous exposure to infected blood. Hepatitis delta virus (HDV) is a small due to defective RNA virus. Hepatitis E virus (HEV) is the causative agent of an acute form of hepatitis identified in 1983. Infection in severely immune compromised patients produces a chronic form of the disease [16].

Besides that, the factor for the cause of acute hepatic disease is the continues use of drugs like paracetamol [13], zidovudine [13], lamivudine [5], CCl_4, thioacetamide and so on [10]. Most of the hepatotoxic by drugs damage hepatic cells mainly by inducing lipid peroxidation and other oxidative stress [12]. More than 900 drugs have been implicated in causing hepatic diseases and it is common reason for a drug to be withdrawn from the market [3]. Currently, there is no specific diagnostic test for drug induced hepatic injury and a means of confidently singling out an implicated drug among potentially many [16]. Due to that, hepatic diseases is a main health problem that challenges to healthcare professionals, pharmaceutical industry and also drug regulatory agencies [10].

3. Herbs as Hepatoprotective Agents

Hepatoprotectives are a group of therapeutic agents including synthetic drugs and natural product which offer protection to hepatic from damage. Herbs are significant source of hepatoprotective drugs. Basically, the evaluation of herbs as hepatoprotective agents due to the therapeutic value, efficacy and toxicity has been done by numerous researchers using *in vivo* and *in vitro* methods [1-3]. The biological properties in herbs such as antioxidant, free radical scavenging, anti-inflammatory, antiviral, choleretic properties also stimulation of hepatic regeneration that could consider as hepatoprotective agents. However, most of the herbs show the hepatoprotection effects to hepatic diseases mainly due to its antioxidant and free radical scavenging properties. The antioxidant helps to prevent from hepatic diseases with the involvement of free radical, especially reactive oxygen species (ROS). Oxidative stress or oxidative demage has been declared to be involved in the development of several chronic hepatic diseases. The reaction between ROS with biomolecules like lipids, protein and DNA may lead to increased risk of chronic hepatic diseases. Due to that, treatment or prevention strategy can be done by retaining balance between ROS and antioxidant [13].

Many ways currently used to evaluate hepatoprotective effect of herbal medicines based on induction factor of hepatic diseases. Common methods used

to evaluate alcohol induction factor of hepatic diseases through the measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST) [2, 12], alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) [14]. ALT and AST are released and spread after hepatic damage occurs, so their activities are most usually used as reliable measurement for clinical monitoring of hepatic diseases. ALP and GGT were plasma enzyme that used to evaluate the hepatopreventive effect. For example, *Curcuma longa* could restore the ALT and AST activities that elevated by alcohol exposure. The hepatoprotective agents of herbal medicine in alcohol hepatic diseases might be associated with antioxidation, anti-inflammation, inhibition of lipid synthesis and increase of fatty acid β-oxidation [12, 14].

The important assessment of drugs induced hepatic damage was studies by measure antioxidant enzymes such as glutathione peroxide (GPX), glutathione-S-transferase (GST), superoxide dismutase (SOD) and catalase (CAT). Usually, *in vitro* study by using hepatic models such as HepG2 model were used to monitor effects of herbs through drugs induced hepatic diseases [14]. Most of the hepatotoxic by drugs were damage hepatic cells mainly by inducing lipid peroxidation [12]. Basically, hepatotoxic by drugs were reduced the feasibility of hepatocytes (a hepatic cell) also reduced the volume and level of bile. By using appropriate phytochemical in herbs such as silymarin, andrographolide, phyllanthin, picroliv, glycyrrhizin and so on the viability of hepatocytes were increased significantly. Besides that, administrations of herbs in drugs induced hepatic diseases were exert a choleretic effect that decreases the cholestasis (failure of bile flow) and lessen retention also increase the excretion of toxic xenobiotics from hepatic. It also stimulated immune system to fight against inflammation.

Table 2 shows list of herbs as hepatoprotective agents with their specific induction factor of hepatic diseases. The specific groups of family also state in the table. Besides that, phytochemicals with class of compounds have been listed in order to study the relation between them as hepatoprotective agent. Currently, numerous researchers have been investigated mechanisms and effects of potential hepatoprotective herbs toward drugs induced hepatic diseases such as CCl_4, paracetamol, D-galactosamine, acetaminophen, rifampirin, thiocetamide, cadmium, amanita phalloides and t-butylhydroproxide. Most of the herbs listed in Table 2 could be used to treat drugs induced hepatic diseases. Generally, silymarin, a flavonolignan from *Silybum marianum* and phyllanthin and hypophyllanthin found in *Phyllanthus niruri* are demonstrated hepatoprotection of hepatic diseases induced by alcohol, viral and drugs. Silymarin shows the hepatoprotection effects to hepatic diseases mainly attributable to its antioxidant and free radical scavenging properties [2, 15, 17]. Silymarin acts as an antioxidant by reducing free radical production and inhibit lipid peroxidation [1, 2, 18]. Silymarin also act as a toxin blockade agent by inhibiting binding of toxins to hepatocyte cell membrane receptors [18]. Specifically, silymarin reduces hepatic diseases cause by paracetamol, acetaminophen, CCl_4, D-galactosamine, amanita phalloides, [2, 3, 18, 19]. Silymarin also react with iron overload, radiation, phenylhydrazine, alcohol and cold ischemia [18]. Although, Silymarin does not have antiviral properties against hepatitis virus, however it promotes protein synthesis and helps in regenerating hepatic tissue, controls inflammation, enhances glucuronidation and protects against glutathione depletion [2, 15]. The hepatoprotective effect of phyllanthus extract from *Phyllanthus niruri* was due to

free radical scavenging activity. It can scavenge superoxides and hydroxyl radicals and consequently inhibit lipid peroxidation [2, 3, 18].

Andrographis paniculata, *Eclipta alba* and *Picrorhiza Kurroa* are exhibited as hepatoprotective agent of hepatic diseases induced by viral and drugs. Andrographolide is pyhtochemicals extracted and isolated from *Andrographis paniculata*. Andrographolide as well exhibited protective effect against hepatic diseases induced by CCl_4, paracetamol, acetaminophen, D-galactosamine and t-butylhydroproxide [2, 3]. It protects hepatic against the hepatotoxins by inhibit lipid peroxidation, malondialdehyde (MDA) and by maintaining high levels of the glutathione (GSH). The class of andrographolide, diterpene lactone exposed the free radical scavenging properties and effect lowering MDA formation. Andrographolide has also shown choleretic activity in in-vivo experiment by stimulating bile production [2]. *Eclipta alba* also has been shown to possess hepatoprotective activity against CCl_4 and paracetamol by significant reduction in the elevated serum transaminase level [11, 20]. *Eclipta alba* was reported to possess hepatoprotective agents as antioxidant, anti-inflammatory, antimicrobial and antiviral properties [20, 21]. Picroliv produces from combination of picroside and kutkoside from *Picrorhiza Kurroa*. Picroliv was found potent against viral hepatitis by showing a promising anti-viral effect [1, 2]. It was able to lower serum lipids, triglycerides and phospholipids. A Picroliv hepatoprotection agent appears to result from a combination of membrane stabilizing and antioxidant properties. Besides that, picroliv has also showed a potent inhibition of hepatocarcinogenesis.

Besides that, curcumin is a main phytochemical of *Curcuma Longa* is showed hepatoprotection of hepatic disease induced by alcohol and drugs. Curcumin has very good antioxidant activity. It inhibits lipid peroxidation. In vivo studies show curcumin has been found to have protective effects on CCl_4 induced hepatic cytochrome P450 (CYP). The CYP isoenzyme inactivation caused by CCl_4 was inhibited by curcumin. Treatment with curcumin on hepatic diseases showed significant improvement and also restoration of lipid profile, marker enzymes and thiobarbituric acid reactive substance to normal. Many herbs have been identified to use as hepatoprotective agent of hepatic diseases induced by drugs such as *Boerhavia diffusa, Glycyrrhiza glabra, Azadirachta indica, Camellia sinensi, Solanum nigrum* and *Amaranthus caudatus Linn*. *Glycyrrhizin glabra* (Glycyrrhizin) has a membrane stabilizing effect and stimulates endogenous production of interferon [1, 18]. Its major class of compounds are triterpene, flavonoids, glycyrrhetic acid, hydroxycoumarins and sterol [18]. The hepatoprotection agent of *Glycyrrhizin glabra* has been attributed to its lipid peroxidation inhibitory, antioxidant and anti-inflammatory [2]. Antiviral properties for the treatment of chronic hepatitis are detected in Phyllanthus. Phyllanthus was found to show hepatoprotective effect by lowering down the content of thiobarbituric acid reactive substance and enhancing the reduced glutathione level and the activities of antioxidant enzymes, GPX, GST, SOD and CAT [9].

Basically, hepatoprotective agent of herbal extract either drugs, viral and alcohol induced hepatic diseases was mainly due as antioxidant and free radical scavenging properties. Phytochemicals with antioxidant property have the ability

to stabilize cell membrane [3]. The potential hepatoprotective of phytochemicals can scavenge superoxides and hydroxyl radicals consequently stabilize cell membrane and inhibit lipid peroxidation ultimately can treat hepatic diseases. Phytochemicals in herbs such as silymarin, phyllanthin, andrographolide and picroliv have potential as hepatoprotection agents against viral (hepatitis A, B, C etc.). Alcohol induced hepatic diseases are attributed to generation of hydroxyethyl radical, which induce lipid peroxidation and thus to hepatic diseases. The polyunsaturated fatty acids of cellular membranes are particularly susceptible to oxidative attack leading to membrane injury and loss of cellular homeostasis. The production of lipid peroxidation in hepatic was found double in presence of alcohol. However, phytochemicals in herbs such as silymarin and curcumin were reduced the hepatic diseases condition significantly. That phytochemicals lessen the alcohol induced hepatic diseases by inhibit lipid peroxidation. Silymarin and curcumin acts as antioxidant to scavenge free radical such as superoxide anions and hydroxyl radicals which are important for the initiation of lipid peroxidation [1, 2]. Besides that, administration of that phytochemicals in alcohol induced hepatic diseases also reduces the level of serum lipids and thiobarbituric acid reactive substances due to either scavenging of peroxides and other activated oxygen species or neutralization of the free radical [2].

4. Mechanisms of Phytochemicals as Hepatoprotective Agents

Phytochemicals can be divided by their structure in nine classes: polyphenolic compounds, terpenoids, glucosinolates, organo-sulfur compounds, phytosterols, saponins, protease-inhibitors and phytoestrogenes. From the Table 2, the classes of phytochemicals compounds that can contribute to hepatoprotection agents are from phenolic compounds (flavanolignans, lignin, phenolic, flavanoids, flavanols) and terpernoids (diterpenic lactoce, triterpenic glycoside, irridoid glycosides, triterpene). Herbs that contain flavonoids are known to possess hepatoprotection agents. Flavonoids exerts a membrane stabilizing action, thus inhibiting lipid peroxidation [22]. Flavonoids, which have proven as antioxidative, antiviral or anti-inflammatory properties, can serve as primary compounds as hepatoprotective drug such as silymarin, phyllanthin, andrographoside, picroside and cucumin. Besides the phenolic compounds, triterpenoids also show hepatoprotective agents through anti-inflammantory properties. Ursolic acid is among the most triterpenoid compounds [23].

Phenolic compounds can be classified into soluble and non-soluble compounds. For example, soluble compounds which are phenolic acids, phenylpropanoids, flavonoids and quinines. While non soluble compounds which are condensed tannins, lignins, cell-wall bound hydroxycinammic acids. Flavonoids is one of particular interest because of its multiple roles in plants and give impact on human health [25]. Flavonoids are one of the largest groups of secondary metabolites. Phenolic compounds exhibit a wide range of physiological properties such as antioxidant, anti-inflammatory, anti-microbial, anti-allergenic etc. It plays an important role in providing protection against pathogens and predators. Structurally, phenolic compounds consist of an aromatic ring, bearing one or more hydroxyl substituent. It ranges from simple phenolic molecules to highly polymerized compounds.

Table 2. List of Herbs as Hepatoprotective Agents.

Induction factor of hepatic diseases	Herbs (Family)	Phytochemical (Class of compound)	Ref.
Alcohol, viral and drugs	*Silybum marianum* (Compositae)	Silymarin, silibinin, silybin and silydianin. (Flavanolignans)	[2, 3, 18, 19]
	Phyllanthus niruri (Euphorbiaceae)	Phyllanthin, hypophyllanthin and niranthin. (Lignans)	[2, 3, 18]
	Andrographis paniculata (Acanthaceae)	Andrographolide, andrographoside, neoandrographolide and Kalmeghin. (Diterpenic lactones and Diterpene)	[2, 3, 12, 19]
Viral and drugs	*Eclipta alba* (Asteraceae)	Wedelolactone, luteolin, and apigenin. (Alkaloids, tannin, flavonoids and phenolic group)	[11, 20, 21, 24]
	Picrorhiza Kurroa (Scrophulariaceae)	Picroside I, Picroside II, III and kutkosides. (Irridoid glycosides)	[1-3, 12]
Alcohol and drugs	*Curcuma Longa* (Zingiberaceae)	Curcumin. (Phenolic)	[1-3, 12, 14]
	Boerhavia diffusa (Nytaginaceae)	Ursolic acids. (Triterpernoid)	[3]
	Glycyrrhiza glabra (Leguminosae)	Glycyrrhizin and saponin. (Triterpene, flavonoids, glycyrrhetic acid, hydroxycoumarins and sterol)	[3, 18]
Drugs	*Azadirachta indica* (Meliaceae)	Azadirachtin and margolone. (Triterpene)	[3]
	Camellia sinensis (Theaceae)	Catechins. (Flavanols)	[3]
	Solanum nigrum (Solanaceae)	Steroidal components. (Flavonoids and terpernoids)	[3, 9]
	Amaranthus caudatus Linn (Amaranthaceae)	(Flavonoids, saponins and glycosides)	[9]
Viral	*Phyllanthus amarus* (Euphorbiaceae)	Phyllanthin. (Alkaloids, flavonoids, lignin, phenol and terpenes)	[18, 19]

Generally, the mechanisms of phenolic compounds act as antioxidant in a number of ways due to their ability to scavenge free radicals, donate hydrogen atoms or electron, or chelate metal ions. The structure of phenolic compounds is a

key determinant of their radical scavenging and metal chelating activity, and this is referred to as structure-activity relationship. Phenolic scanvenge hydroxyl group are good hydrogen donor in which hydrogen-donating antioxidants can react with reactive oxygen and reactive nitrogen species in termination reaction and at the same time break the cycle of generation of new radicals [26]. Subsequent interaction with the initial reactive species, a radical form of the antioxidant is produced, having a much greater chemical stability than the initial radical. The chelate metal ions involved in the production of free redicals. Phenolic structures often have the potential to strongly interact with proteins, due to their hydrophobic benzenoid rings and hydrogen-bonding potential of the phenolic hydroxyl groups. This gives phenolics the ability to acts as antioxidants also by virtue of their capacity to inhibit some enzyme involved in radical generation [27].

5. Conclusions

It is showed that many herbs have potential to treat different induced of hepatic diseases especially *silybum marianum* and *phyllanthus niruri*. Phytochemicals obtained from herbs can provide as suitable main compounds for effective hepatoprotective agents such as antioxidant, anti-inflammatory and antiviral properties. Herbs either single or combination should possess adequate efficacy to treat severe induced hepatic diseases caused by alcohol, viral and drugs. The class of phytochemicals in herbs such as flavanoids and terpernoids received extensive attention due to their diverse pharmacological properties especially in hepatic diseases. Antioxidants play crucial role in inhibiting and scavenging radicals which eventually providing protection to human against hepatic diseases. In the future, the effective formulations for the combinations of phytochemicals have to be developed using original medical plants which proper pharmacological experiments and clinical trials. These combinations will promote to treat various inducing factors of hepatic diseases.

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