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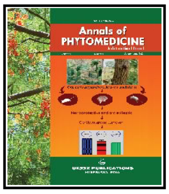

Review Article : Open Access

Bioactive compounds from medicinal plants in liver disease treatment : A review

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Abstract

Liver is the one of the most important organ in the body which performs variety of regulatory as well as metabolic activities. Currently, the worldwide reported mortality is increasing due to hepatic complications such as liver cirrhosis, viral hepatitis, fatty liver diseases and hepatocarcinoma. Limited efficacies as well as the major side effect of existing drugs are the limitations for the treatment of liver diseases. Therefore, there is a need for an alternative treatment for treating liver diseases. Hence, the herbal medicine or plant mediated medicines are gained much attention due to their use in some regions or countries. Phytoconstituents of herbal origins were claimed and possess effective alternative therapy for hepatoprotection. A wide variety of chemical components and extracts containing alkaloids, polyphenols, coumarins, glycosides, terpenes and lignins. Many polyherbal formulations containing multiple herbal components also effective in the treatment of hepatic pathophysiological conditions. Here, we summarized the phytochemicals which were used for the treatment of liver diseases such as hepatitis, cirrhosis, fatty liver diseases and liver cancer.

1. Introduction

In the human body, liver is the detoxifying organ and is the most significant organ which performs various primary role in regulatory processes such as secretion, storage and metabolism (Adewusi and Afolayan, 2010; Jyothilekshmi, 2020) and also involved in the biochemical processes like growth, supply of nutrient and energy as well as reproduction (Ahsan *et al.*, 2009). As a theme of reality, many of the unanswered conditions in hepatology can be predicted for differences in the inflammatory process. Subsequently, the inflammation in the hepatic region leads to the development of liver diseases (Tacke, 2017; Michelotti, 2013). Hepatic or liver diseases occurred due to the above-mentioned functions which continued to pose the serious health threat to the public worldwide. It is causing a huge economic trouble to the society by means of varying hepatic pathology like steatosis, cirrhosis to hepatocellular carcinoma and hepatitis resulting high morbidity and mortality (Peter, 2014; Jia *et al.*, 2019). Liver disease is a condition that could harm the tissues, cells, structures, liver functions and these damages are caused by various biological factors including microbes and chemicals as well as autoimmune diseases (Casafont *et al.*, 2008; Deshwal *et al.*, 2011; Amengual *et al.*, 2000). The liver diseases are caused by alcohol abuse, hepatitis due to viral infection and deregulated metabolic activity (Li *et al.*, 2015) along with excessive inflammation, oxidative stress and disruption of immune response (Li *et al.*, 2016). Surprisingly, globally, 25% of adults are affected by non-alcoholic fatty liver disease and also 75 million are identified with alcohol associated disorders (Friedman, 2008). Unfortunately, the occurrence of hepatitis due to viral infection is high but in worldwide, roughly 1.16 million deaths were reported every year for cirrhosis and nearly one million deaths were counted for liver cancer (Sumeet *et al.*, 2019; Mokdad *et al.*, 2014). Altogether, 500 million populations were affected by liver disorders that were estimated by World Health Organization (Al-Asmari *et al.*, 2014). The treatment for the liver disease is existing, but their efficacy is still limited in the developing countries. Therefore, there is a need to discover the new approach to successfully avoid the progress and the development of liver diseases. The major pathological conditions of liver which leads to hepatotoxicity is due to free radicals. Upon bioactivation and biotransformation of the drugs, nutraceuticals, supplements and food reactive oxygen species is generated and causes macromolecular degradation through protein dysfunction. It eventually causes DNA damage. However, before the events happen, a series of pathological process initiate and make the way for hepatoxicity. The liver necrosis or hepatoxicity happens in background of inflammation. The primary cause of liver necrosis is inflammation in swelling, ATP depletion, immune dysfunction and inflammatory cytokines (TNF-α (tumour necrosis factor) and interleukin) trigger. Additionally, the immune functions of liver sinusoidal endothelial cells were altered during hepatoxicity events. Toll-like receptors and nucleotide-binding domain-like receptors triggers the immune reactions to lead pathophysiological conditions of liver. These altogether causes activation of nuclear factor NF-kB and triggers the inflammatory cytokines and chemokines. Finally, the liver enzyems were elevated during the initial stage of hepatoxicity and blood level enzymes elevates abnormally.

Medicine from the plant source might provide the reasonable treatment for the existing liver diseases since considering their safety, availability; economical as well as eco-friendly because of these abilities, the herbal or plants gained much attention in the medical

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field all over the world (Izzo *et al*., 2016) as the phytochemicals from various sources including vegetables have been widely used (Pushpangadan, 2015). Phytoconstituents are also increasingly emerging source for the treatment of human ailments (Husain, 2021; Mehrotra, 2021; Parveen *et al*., 2020). Many phytochemicals have been clinically available as potent hepatoprotective agents against commonly occurring liver diseases. Hepatoprotective activity of various plants were studied and exhibited effective treatments. Combination of phytochemicals exerts optimized hepatoprotective effects. Curcumin and quercetin in combination on cyclophos-phamide induced hepatotoxicity (Yadav *et al*., 2021). Hence, in this review, hepatoprotective activities of phytochemicals or compounds are summarized.

2. Phytocompounds against hepatitis

Hepatitis is the enlargement of liver caused by the viral infection or auto immune diseases or substances containing toxic material like drug or alcohol. Among the liver diseases, viral hepatitis is most common which may develop to fibrosis and cirrhosis when left untreated (Ma *et al*., 2014). Owing to restricted treatment effect of existing medicine, alternative medicine was developed worldwide. In support of this, most important compound baicalin from *Scutellaria baicalensis* which was used as traditional medicine in China has various biological activities like liver diseases. The baicalin was more potent against hepatitis (Jin *et al*., 2021). Consequently, a potent compound glycyrrhizin showed activity against hepatits was isolated from *Glycyrrhiza uralensis* Fisch in China as well as Japan. Since 1948, due to the potent activity exhibited by the glycyrrhizin, it was approved as injection for the treatment of allergic information and again it was accepted for chronic hepatitis from 1979 (Kumada, 2002). In recent times, glycyrrhizin was found to be active against hepatits C virus (Matsumoto *et al*., 2013). Similarly, another flavonoligans mixture compound silymarin was extracted from *Silybum marianum* displayed a potent activity against hepatits (Kidd *et al*., 2005). The subtropical plant called *Phyllanthus niruri* L used as traditional medicine and extensively present in China and south Asia showed activity against hepatitis and also exhibited a wide variety of biological activity (Liu *et al*., 2014; Ibrahim *et al.*, 2013; Amin *et al.*, 2012). The *Polygonum cuspidatum* Willd. ex Spreng was used to treat hepatitis and other diseases which was widely distributed in Asian countries (Zhang *et al*., 2013) and it is one of the traditional medicine in China. The main compound responsible for hepatoprotective property was anthraquinones (Peng *et al*., 2013).

An alkaloids matrine and oxymatrine were isolated from the *Sophora flavescens* Aiton and have been used for hepatitis. The matrine showed activity 200 mμg/ml and oxymatrine showed 100 mμg/ml (Ma *et al*., 2013). A novel phytochemical periplocoside A was isolated from *P. sepium* and acted against auto immune associated hepatitis (Wan *et al*., 2008). The compound baicalin was identified from *Scutellaria baicalensis* Georgi which was able to defend the liver cells from stress through up regulating the liver fatty acid binding protein (Ai *et al*., 2011). Similarly, the frequent use of herbal medicine is *Schisandra chinensis* identified from China against hepatitis. The reverse pharmacological studies were confirmed that, *Schisandra chinensis* has the antihepatitis activity (Yim *et al*., 2009). Another group identified and examined the seven unfamiliar and familiar ligans and found that two of them showed excellent antihepatitis activity (Xue *et al.*, 2015). In Chinese traditional medicine, frequently used herbs is *Astragalus membranaceus* for more than several centuries. The herbs were analysed for their phytochemicals and found that saponins and flavonoids are the major components in the plant (Cai *et al*., 2015; Yu *et al*., 2014).

3. Phytocompounds used for treatment of fatty liver disease

The fatty liver disease is the reversible pathological procedure in which huge numbers of triglyceride fat vacuoles are accumulated in the liver cells, it was generally induced by metabolic disorders as well as overuse of alcohol consumption (Bobe *et al*., 2004). The compound called curcumin was identified from turmeric and evaluated for variety of bioactivity. The curcumin was exhibited the potent activity against fatty liver disease (Xu *et al*., 2018; Baziar, 2020). Another compound allicin was identified in garlic, showed the activity against fatty liver diseases (Panyod *et al*., 2020). Several plants like *Rhodiola rosea*, *Silybum marianum* and *Panax ginseng* producing salidroside a phenolic compound, silymarin (lipophilic compound), ginsenosides were used for treating the alcoholic and non-alcoholic fatty liver diseases (Sahin *et al*., 2020; Yao *et al*., 2020). Another interesting plant material beverage is coffee contains caffeine, cafestol, kahweol showing a protective activity against fatty liver disease (Shokouh *et al*., 2018).

One of the most important compound used in Chinese traditional medicine is berberine which coating quaternary ammonium salt was identified from the berberis plant. This compound was effective against in eliminating the triglycerides accumulation in liver cells (Fan *et al*., 2013). In China and Japan, *Gynostemma pentaphyllum* was used to treat the fatty liver diseases by lowering cholesterol (Wang *et al*., 2013). Further, a study revealed underlying mechanism of action against fatty liver disease is the increasing the production of nitric acid, whereas it reduced the oxidative damage in the liver cells (Muller *et al*., 2012). The *in vitro* and an *in vivo* activity of penta-oligogalacturonide compound identified from *Crataegus pinnatifida* Bunge was studied against non alco-holic liver disease (Shi *et al*., 2012). Another steroidal compound dioscin identified from *Dioscorea opposita* Thunb has the ability to fight against non-alcoholic fatty liver disease (Li *et al*., 2014). Moreover, a trihydroxybenzoic acid containing gallic acid was recognised from pericarp of *Punica granatum* L. displayed a potent activity against fatty liver disease by regulating the choline, aminoacid metabolism (Chao *et al*., 2014).

4. Phytochemicals for the treatment of cirrhosis

Liver cirrhosis is the situation wherein the liver function did not work properly owing to long duration of liver damage. Limited efficacy associated with existing medicines resulting high morbidity and mortality (Sivanathan *et al*., 2014). Similary, Chinese herbal medicines played a vital role in decreasing the death date of liver cirrhosis after treatment with medicine (Tsai *et al*., 2020). Consequently, the important phytochemical berberine was studied for their hepatoprotective property. The results revealed that, the berberine showed the remarkable activity against liver cirrhosis by inhibiting the AMPK pathways (Li *et al*., 2014). The isoflavones compound puerarin recognized from *Pueraria lobata* was evaluated for hepatoprotective property. The results revealed that, it has the promising activity against liver cirrhosis by promoting the metabolic function, ALT, AST level reduction (Guo *et al*., 2013). Another study from Li and his team group revealed the mechanism of action of puerarin against liver cirrhosis mediated through the down regulation of TNF alpha and NF-kB gene expression. It can also induce apoptosis on liver cells (Li *et al*., 2013). *Saururus chinensis* is one of the important Chinese medicines used to treat various disorders. In the reverse pharmacology, the extract of *Saururus chinensis* has decrease the liver indexes resulting promising hepatoprotective property against liver cirrhosis (Kwon, 2014).

In vitro and *in vivo* studies of glycyrrhizin effect on liver cirrhosis was evaluated. The results revealed the anticirrhosis effect of glycyrrhizin by inhibiting the binding affinity of NF-kB cells. The clinical study revealed that, glycyrrhizin with 12 weeks treatment showed the 50 per cent of decrease in the liver indexes and also no side effects were observed (Qu *et al*., 2015). Another compound, silybinin was observed for its anticirrhosis effect and exhibited the potent effect by inducing the biogenesis of mitochondria in liver cirrhosis. Keeping this in mind, the mechanism was deciphered for silybinin against liver cirrhosis and found that, it was preventing the reactive oxygen species and inhibit the oxidation of liver cells (Serviddio *et al.,* 2014). A compound saikosaponin A was identified from *Bupleurum chinense* studied for its hepatoprotective activity and found that, it has been showing the protective ability to liver cirrhosis. The results revealed that, after treatment with the compound decrease the development of liver cirrhosis y down, regulating the plasma aspartate and alanine aminotransferase activities (Wang *et al.,* 2013). The salvianolic acid B identified from *Salvia miltiorrhiza* Bunge showed the antiliver cirrhosis ability by inhibiting intracellular signal transduction (Parajuli *et al*., 2015). The methanolic extracts of *Scutellaria baicalensis* Georgi importantly reduce the liver cirrhosis by inducing cell arrest in the cell cycle of liver cells (Sun *et al.,* 2010).

5. Phytochemicals for the treatment of liver cancer

Liver cancer prevalence is more in the industrialized countries and it is estimated that, sixth most frequently identified cancer in worldwide resulting high morbidity and mortality (Prasad *et al*., 2014). Further more, the pharmacological studies of two alkaloidal compounds *Coptidis rhizoma* and berberine have been established the promising anti canceractivity against hepatocellular carcinoma. The alkaloids can suppress vascular endothelial growth factor (VEGF) secretion and inhibit the eEF2 resulting blockage of protein synthesis (Tan *et al*., 2014). The *Bupleurum chinense* DC was when combined with chemotherapy, the frequency of micronuclei was increased and damage in the liver cancer cells DNA was observed. Same way, saikasaponin was combined with chemotherapy showed a excellent anticancer activity against liver cancer cells by inducing apoptosis with the activation of caspases family resulting fragmentation in the DNA (Wang *et al*., 2014). The extract of *Salvia miltiorrhiza* Bunge can protect the human liver cancer cells by inhibiting the plasminogen activator. A further study revealed that, 1-(Tanshinones) is the major compounds present in the *Salvia miltiorrhiza* Bunge showed activity against doxorubicin resistant liver cancer cells. Another compound called tanshinone IIA showed the anti-cancer activity against liver cancer cells (Rui *et al*., 2014). Recently, the important ingredient called elemenes which are natural occurred compound in *Curcuma aromatic* salisb. The compounds were evaluated the anticancer activity against liver cancer cells by inducing the cell apoptosis (Bao *et al*., 2012). Another group found that, elemenes can also suppress the liver cancer cells by histone H1 protein increased expression (Mao *et al*., 2013).

The extract of *Brucea javanica* has been showed the anticancer activity against liver cancer cells by inducing apoptosis through regulating the mitochondrial dependent pathway and activates caspase family and it also inhibits the proliferation of HepG2 cells (Lau *et al.*, 2005). The quinoline compound camptothecin was identified the bark or stem of *Camptotheca acuminata* Decne which was widely distributed in China and the compound was exhibited the anticancer activity against liver cancer cells. The activity was achieved through the suppression of the cell growth (Jayasooriya *et al*., 2014). A compound was isolated from the ginger family; curcumin is a dairy as well as heptanoid compound from turmeric was used generally in food preparation. Because of its toxic less nature, it was evaluated for anticancer property and displayed a extraordinary *in vitro* and *in vivo* anticancer activity. The curcumin showed a prominent activity when used in alone or in combination with commercially used drugs like cisplatin and doxorubicin through cell multiplication inhibition and induces apoptosis in liver carcinoma cells (Notarbartolo *et al*., 2005; Wang *et al*., 2008; Zhao *et al.*, 2019). Another dietary compounds like reveratrol (Zhang *et al.*, 2020), silybin (Zhang *et al*., 2013), lycopene (Thomas *et al*., 2020), emodin (Zhou *et al*., 2019), octopamine (Rawat *et al*., 2018), phloretin (Saraswati *et al*., 2019) and also caffeine (Wang *et al.*, 2019) were used to treat the liver carcinoma cells. Moreover, based on the previous report most of anticancer drug are from natural sources (Rawat *et al*., 2018).

6. Conclusion

This review provides the current status of phytochemicals which were used for the treatment of liver diseases. This review gives the detail about the medicinal plant or phytochemicals were active against liver diseases by inhibiting or reducing the metabolic pathways, reducing oxidative stress, removal of viral infection and inhibiting cell growth. Many plants are needed further studies to confirm their activity.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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