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Review Article

A Review On Hepatoprotective Efficacy Of Various Phytochemicals

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ABSTRACT

The plant kingdom has been a very important resource to offer us natural products which are meant for treating many diseases with lesser side effects. Since the liver performs many vital functions in our human body, the malfunction in the liver causes a severe threat to public health. The challenges such as stimulation of affected liver function, lack of complete protection of the liver, degeneration of liver cells and inefficient nature of current treatment therapy often delay the drug discovery in liver diseases. Despite the setback, natural products derived from plant resources have partly provided some relief in identifying liver protecting compounds. For instance, silymarin is a naturally obtained milk thistle, containing flavonolignans. Research studies emphasized a hepatoprotective property of silymarin in acute and chronic hepatic dysfunction. Multiple pharmacological mechanisms behind hepatoprotective efficacy of silymarin were reported including stimulation of superoxide dismutase expression and its activity, inhibition of entry of toxins into the liver, enriching glutathione concentrations, improving liver protein production and blocking lipid peroxidation process. A lot of factors should be considered to get a novel natural compound that possesses hepatoprotective property. Parameters such as extraction procedure, parts of the plant and use of reagents in separation technique are very critical in the isolation of the active natural product.

INTRODUCTION

Liver is a critical component in the human body, which is involved in many biological processes such as the metabolism of carbohydrates, protein, and lipids, detoxification of exogenous and endogenous agents, secretion, and storage. In addition to the above-mentioned functions, the liver is involved in supplying nutrients, delivering energy, growth and reproduction. The diverse functions of the liver underscore the importance of

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liver related diseases and their treatment options. Short-term and long-term liver dysfunction account for poor work-life balance, global economic issues, and burden to human society (Subramoniam and Pushpangandan, 1999). The treatment of liver diseases poses a copious number of challenges and obstacles including limitations and ineffectiveness of current therapy. Important properties of the efficacious drug meant for liver diseases including regeneration of liver cells, induction of liver function and complete protection to the liver have been lacking in current hepatoprotective therapy (Adewusi and Afolayan, 2010). Consequently, a quest for the discovery of novel hepatoprotective compounds that exhibit more efficacious and less toxic has started a few decades ago. However, efficacious liver protective drugs are still elusive. Utilizing plant resources or herbal medicines is one of the best approaches to identify hepatoprotective compounds, which have many advantages such as low adverse effects (Madrigal-Santillan et al., 2014). Liver diseases or hepatic diseases are characterized by the disruption in the function of cells, tissues and components of the liver itself. The critical functions of the liver could be affected by many parameters – 1) drug compounds including paracetamol, isoniazid and other antitubercular drugs, 2) toxic chemical molecules such as carbon tetrachloride, lipopolysaccharide, thioacetamide, dimethyl nitrosamine and D-galactosamine, 3) autoimmune disorders such as cirrhosis and hepatitis, 4) biological vectors such as parasites, bacteria and viruses 5) extreme alcohol consumption (Casafont-Morencos et al., 2008; Amengual-Guedan and Rodriguez Sanchez, 2000; Deshwal et al., 2011).

Silymarin – Hepatoprotective plant derived compound:

Silymarin is used as a hepatoprotective phytochemical in various liver disorders. Silymarin is chemically a flavonolignan containing scaffold (figure 1), isolated from Silybum marianum or milk thistle (Pradhan and Girish, 2006; Abenavoli et al., 2010). The fruits of milk thistle were used to isolate a cluster of compounds, known as silymarin. The chemical compounds found in silymarin are silydianine, silybin A, silychristine B, silychristine A, silybin B, isosilybin B and isosilybin A (Madrigal-Santillan et al., 2013; Hamid et al., 1983; Morazzoni and Bombardelli, 1995; Lee and Liu, 2003; Ligret et al., 2008) while silymarin is the combination of lignan and flavonoids. Several studies reiterated that silymarin is used as a hepatoprotective compound in acute and chronic hepatic diseases. The hepatoprotective efficacy of silymarin falls in different mechanisms – induction of superoxide dismutase expression and its activity, blockade of entry of toxins into the liver, enhancing glutathione concentrations, improving liver protein production and preventing lipid peroxidation process (AbouZid, 2012). High doses of paracetamol and few analgesic drug compounds possess liver necrosis. The hepatoprotective efficacy of silymarin was explored in paracetamol treated Balb/c mouse models. Pretreatment of 100 mg/kg silymarin in Balb/c mice, followed by 300 mg/kg paracetamol administration. Histological and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) investigation results showed that silymarin produced a remarkable decrease in paracetamol induced liver malfunction. Silymarin was found to reduce heme oxygenase-1 (HO-1) stimulation, in vitro mitochondrial superoxide synthesis, elevated nitrosative stress, levels of p-JNK and GSSG, thereby minimizing superoxide synthesis. On the other hand, the reduction of paracetamol induced CYP2E1 expression, and its activity was not affected by silymarin treatment. Both silymarin treated and control paracetamol treated groups were reported to possess elevated inflammatory genes and neutrophil filtration at the T12

timepoint. However, at T24 the inflammation was reduced in the silymarin treated mice group. Paracetamol toxicity targeted many parts of the liver through the necrosis cell death pathway where it was partly reduced by pretreatment of silymarin. This protective role of silymarin might be via scavenging efficacy of silymarin and decreased levels of peroxynitrite and superoxide (Papackova et al., 2018).

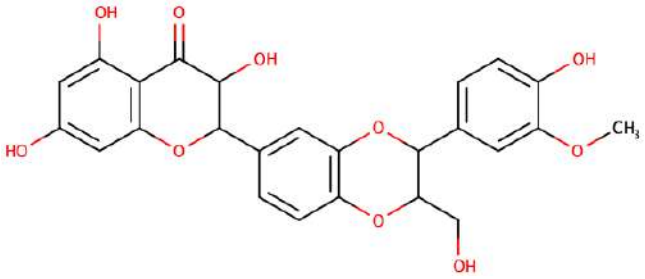

Figure 1. Chemical structure of silymarin

Naturally occurred hepatoprotective plants, various extracts and phytochemicals:

Methanol and petroleum extracts (200 mg/kg and 400 mg/kg) of Glycosmis pentaphylla lessened the abnormal concentration of total protein, total bilirubin, ALT, AST and alkaline phosphatase (ALP) in Swiss albino mice. In particular, methanolic extract at 400 mg/kg protected membrane integrity and modified the toxicity of hepatocytes caused by paracetamol overdose (Nayak et al., 2011). The leaf extracts of the artichoke were investigated for their hepatoprotective effects compared with silymarin treated mouse models. The mice group treated with paracetamol revealed a notable rise in ALP, AST, ALT, proliferative cell nuclear antigen (PFCNA), malondialdehyde (MLDA) and liver weight while a significant reduction of glutathione reductase (GTR) was observed as compared to the control group. This malfunction caused by paracetamol toxicity was attenuated in the mice group treated with artichoke leaf extracts, silymarin and both. Pretreatment with artichoke leaf extracts, silymarin and bothin mice with paracetamol administration reduced the expression of PCNA (Elgarawany et al., 2019). Methanolic extract of rhizome and root of Smilax zeylanica L. was found to minimize the escalated concentration of total protein, total albumin, total bilirubin, ALP, AST and ALT, and increased liver weight in Wistar rats. In addition, the methanolic extract had prevented serum markers leak and attenuated the toxic insult to the hepatocytes caused by a high dose of paracetamol (Murali et al., 2012). In another study, the methanolic leaf extract of Cyathea gigantea (100 mg/kg and 200 mg/kg) minimized the increased concentrations of alkaline phosphatase (ALP), total protein, total bilirubin, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) while it also reversed the paracetamol toxicity to liver cells (Madhu Kiran et al., 2012). The root fractions of Hippocratea Africana (Willd.) Loes. Ex Engl reduced the elevated concentrations of ALP, AST, ALT, total protein, total cholesterol, total bilirubin, total albumin, direct bilirubin and antioxidants enzymes such as catalase transferase (CAT), glutathione (GSH), glutathione peroxidase (GPx) and superoxide dismutase (SOD) (Okokon et al., 2013). Increased levels of ALT, AST, ALP, blood urea nitrogen and albumin were reduced by the methanolic extract of Woodfordia fruticose flowers in paracetamol mediated hepatotoxicity in rats. Moreover, methanolic flower extract inhibited the paracetamol induced oxidative insults in rat liver via restoring the reduced glutathione and reducing depletion of total protein (Baravalia and Chanda, 2011). C57BL/6 mice treated with the extracts of berries of Sea buckthorn or HippophaerhamnoidesL. were found to reveal the reduced concentrations of AST and ALT against paracetamol mediated toxicity. On the other hand, the extracts enhanced the levels of reduced nitric oxide, SOD, SOD-2, inducible nitric oxide synthase, GSH, GSH-Px. In addition, Sea buckthorn inhibited paracetamol induced JNK

phosphorylation while the proportion of Bcl-2/Bax was increased. The berries extracts minimized the expressional levels of Keap1 and enhanced the nuclear translocation of Nrf2 and its target genes such as HO-1 (Wang et al., 2018).The hepatoprotective effects of Pandanus odoratissimus Linn. seed extracts were examined in Sprague-Dawley rats. Various concentrations of methanolic seed extracts of Pandanus odoratissimus (300 mg/kg, 600 mg/kg and 900 mg/kg, 14 days once a day) or 200 mg/kg silymarin were injected into paracetamol mediated hepatotoxic rats. The seed extracts reduced the serum concentrations of direct bilirubin, total bilirubin, γ-glutamyl transferase (GGT), ALP, SGOT and SGPT dose-dependently. In addition, inhibition in the reduction of serum protein and albumin levels was noted (Sinaga et al., 2021). In another study, an ethanolic root extract of Pandanus odoratissimus (200 mg/kg, 400 mg/kg 7 days oral administration) was investigated for their antihepatotoxic efficacies in Wistar rats while 100 mg/kg silymarin was used as a positive control. Dose-dependent hepatoprotective effects were reported that were compared with the silymarin treated group (Mishra et al., 2015). The polar butanol fraction of methanolic extracts of Neanotis wightiana was investigated for novel phytochemical constituent and hepatoprotective potential in carbon tetrachloride induced hepatotoxicity rats. Three compounds (two triterpenoids oleanolic acid and ursolic acid, along with novel compound) were isolated from the butanol fraction of methanolic extracts. Neanoside B, as a naphthalene diglucoside, was identified and its chemical structure was supported by spectroscopic analysis and chemical studies. Significant in vivo dose-dependent (5 mg/kg, 10 mg/kg and 20 mg/kg) hepatoprotective activity of neanoside B was observed in hepatotoxic rats. The novel phytoconstituent was found to reduce the escalated levels of total bilirubin, ALP, SGPT and SGOT through enhancing antioxidant properties. The hepatoprotective efficacy of neanoside B (chemical structure provided in figure 2) at 20 mg/kg was comparable with 100 mg/kg silymarin (Das et al., 2017).

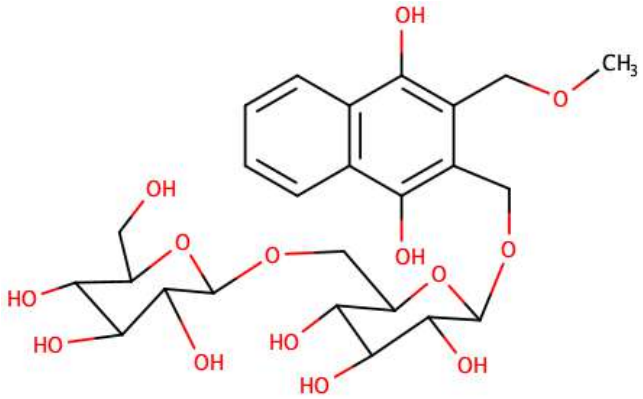

Figure 2. Chemical structure of neanoside B

A research study with extract of Anacyclus pyrethrum Linn was carried out to evaluate the hepatoprotective effects in antitubercular combined drugs (isoniazid and rifampicin) induced hepatotoxic rats. Silymarin (100 mg/kg) as a positive control, different concentrations such as 200 mg/kg, 400 mg/kg of Anacyclus pyrethrum Linn were administered to rats. It was found that extracts diminished the serum levels of lactate dehydrogenase (LDH), cholesterol, SGPT, SGOT, ALP, liver weight, total protein, and albumin. The hepatoprotective activity of extracts at 400 mg/kg was comparable with silymarin (Usmani et al., 2016). The hepatoprotective effect of ethanolic extract of Fagonia schweinfurthii (Hadidi) was studied in carbon tetrachloride mediated hepatotoxic rats and HepG2 cell lines.Carbon tetrachloride induced hepatotoxicity and increased serum concentrations of total bilirubin, ALP, AST, ALTwas partly blocked by the extract of fagonia schweinfurthii (Pareek et al., 2013).The study on the antihepatotoxicity efficacy of Citrullus colocynthis fruits was conducted in paracetamol induced hepatotoxic rats. The methanolic extract of Citrullus colocynthis fruits at 300 mg/kg dose was found to prevent the augmented serum levels of SGPT, SGOT, total bilirubin, and ALP

(Vakiloddin et al., 2015). The ethanolic extract of Nigella sativa was examined for its hepatoprotective activity in paracetamol induced hepatotoxic rats. Studies showed that Nigella sativa ethanolic extract significantly reduced the escalated concentrations of SGOT, SGPT, ALP and total bilirubin when compared to rats treated with paracetamol mediated hepatotoxicity (Kushwah et al., 2014). Aqueous fractions obtained from leaf extracts of Basella alba (100 mg/kg once a day oral administration) remarkably reduced the raised serum levels of ALP, SGOT, SGPT, bilirubin, and total proteins in paracetamol mediated hepatotoxic albino rats. The hepatoprotective efficacy was comparable and even superior to silymarin treated rats (Das et al., 2015). The alcoholic and aqueous extracts of stem parts of Musa paradisiaca were examined for their antihepatotoxic activity in paracetamol as well as carbon tetrachloride induced hepatotoxicity rat models. The alcoholic and aqueous extracts at 500 mg/kg concentration significantly prevented the escalated levels of ALP, SGPT, SGOT and total bilirubin in hepatotoxic rats (Nirmala et al., 2012). The evaluation of the hepatoprotective activity of Daucus carota was conducted. In this study, methanolic extracts of seeds obtained from Daucus carota were investigated in thioacetamide mediated (100 mg/kg) oxidative stress and hepatotoxicity rat models. The concentrations of ALP, SGPT and SGOT were reduced significantly in the rat group pretreated with thioacetamide. In addition, antioxidant effects of seed extracts were exhibited, through the induction of CAT, glutathione-S-transferase (GST), GSH, GPX and SOD (Singh et al., 2012). The extraction procedure of Acrocarpus fraxinifolius Arn. using ultra gas GC chromatographic analysis, along with its hepatoprotective potential was explored in albino rats. Paracetamol was administered to induce hepatotoxicity in albino rats. The chemical compounds isolated in GC chromatographic analysis were lupeol, labda-8-13-dien-15-oic acid, α-tocopherol, phytol and squalene. The extract at 500 mg/kg showed the hepatoprotective effects in rats through the reduction of elevated levels of SGOT, SGPT, ALT, AST, liver lipid peroxidation, total lipid, increased body weight, total protein and total bilirubin (Abd El-Ghffar et al., 2017).

CONCLUSION

This review article has mainly focused on plants extracts and phytochemicals that could exhibit hepatoprotective effects in murine models and some cell lines. Different parts of the plants were utilized in the experimental sections of studies and evaluated for their antihepatotoxic potentials. Murine models and other in vivo models have generally been administered with high doses of paracetamol, carbon tetrachloride, thioacetamide and antitubercular compounds to cause hepatotoxicity. Some of the studies did not have appropriate positive control such as silymarin whereas the effects of different concentrations of extracts compared with hepatotoxic rats. Various parts of the plants could be used to isolate novel natural phytoconstituents that show potent hepatoprotection as well as fewer adverse effects. In summary, this article provides antihepatotoxic activities of a few phytomedicines and several extracts of plants via stimulating antioxidant mechanisms. Further research studies are warranted to optimize and establish efficacy, safety and definite mechanism of action or pharmacological action, isolation of active phytoconstituents and evaluation of hepatoprotective effects using an appropriate animal model. This should be followed by clinical studies to explore the safety and efficacy of natural products in human volunteers in the treatment of liver diseases.

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CONFLICTS OF INTERESTS:

Present study does not contain any conflict of interest.

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