WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 6, 188-197. Review Article ISSN 2277– 7105

HERBAL FLAVONOIDS IN TREATMENT OF HEPATIC DISEASES: A REVIEW

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Article Received on
25 Feb. 2019,
Revised on 14 March 2019,
Accepted on 04 April 2019
DOI: 10.20959/wjpr20196-14336

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ABSTRACT

Liver is a vital organ of paramount importance which is the largest glandular organ in the body, located under the diaphragm in the upper right abdomen. In the anatomy and physiology the parts which make up liver are lobules, hepatic duct, portal vein and hepatic vein, inferior vena cava, other organs: Gallbladder and pancreas; Gastrointestinal blood flow and blood flow to the liver takes place. The liver performs many essential functions related to metabolism, immunity, and the storage of nutrients within the body; detoxification, protein synthesis and production of biochemical necessary for digestion and synthesis as well as break down of small and complex molecules. Hepatic diseases is a term for a collection of conditions, diseases, and infections that affect the cells, issues structures, or functions of the liver. Flavonoids are a class of plant and fungus secondary metabolites. Chemically, flavonoids have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and a heterocyclic ring (C). They are divided into seven classes: Anthocyanidins, proanthocyanidins, flavones, flavonols, flavan-3-ols, flavanones, isoflavones. Herbs which are rich in flavonoids are mentioned with their classes, dietary sources and uses. Example, rutin are found in green tea, grape seeds, citrus fruits etc and are used to treat cancer, osteoarthritis and heomorrhoids. Hepatic diseases, containing a wide range of hepatic pathologies from steatosis, hepatitis, and fibrosis to hepatocellular carcinoma (HCC), are leading causes of morbidity and mortality worldwide and have caused huge socioeconomic burdens. The main etiologies of hepatic diseases are cancer, NAFLD, hepatitis C, alcoholic liver disease, fibrosis. In this review, we aim to summarize and update the existing evidence of herbal flavonoids in the prevention and treatment of various hepatic diseases, while special attention is paid to the action mechanisms and were the signs & symptoms, pathophysiology and sources from which particular diseases are cured.

KEYWORDS: Hepatic diseases, anthocyanidins, heomorrhoids, steatosis.

The largest internal organ in the body. Located under the diaphargm in the upper right abdomin. The word hepatic refers to liver. Anatomy and physiology of liver: Divided into four lobules made up of many lobules, Blood from aorta delivered to the liver via the hepatic artery, Portal vein delivers blood from intestine to liver, Portal blood circulates through liver; transported into the inferior vena cava by the hepatic veins, Specialised hepatic cells allow the liver to carry out many critical function.

Bile production, absorbing and metabolizing bilirubin, supporting blood clots, fat metabolization, metabolizing carbohydrates, vitamin and mineral storage, helps metabolize proteins, filters the blood, immunological function, production of albumin, synthesis of angiotensinogen these are the functions of liver.

Fascioliasis, cirrhosis, hepatitis, alcoholic liver disease, primary sclerosing cholangitis (PSC), fatty liver disease, gilbert's syndrome, liver cancer are the different types of hepatic diseases.

Flavonoids: Flavonoids are a group of plant metabolites thought to provide health benefits through cell signalling pathways and antioxidant effects. These molecules are found in a variety of fruits and vegetables.

Different herbal flavonoids and their uses

S.no	Flavonoids	Class	Sources	Uses
1.	Peonidin	Anthocynidins	Cranberries, blueberries, plums, grapes, cherries, sweet potatoes	Diabetes, lung cancer
2.	Cyanidin	Proanthocynidins	Tea, cocoa, grape juice, cranberries.	Cardiovascular diseases and cancer
3.	Luteolin	Flavones	Celery, broccoli, green pepper, parsley, thyme, dandelion, chamomile tea, olive oil, rosemary, navel oranges	Cancer, allergies, asthma
4.	Rutin	Flavonols	Green tea, grape seeds, red pepper, apple, citrus fruits, berries, peaches	Cancer, osteoarthritis, heomorrhoids
5.	Epicatechin	Flavan-3-ol	Milk, chocolate, commercial, reduced fat	Diabetes, cardiovascular diseases.
6.	Hesperdin	Flavanones	Bitter orange, lemon, petit grain	Chemotherapy, atherothrombotic diseases
7.	Daidzein	Isoflavones	Soyabeans, tofu	Prostate cancer, osteoporosis
8.	Arbutin	Chalcones	Strawberries, pears, bearberries,	Hepatic cancer.[1],[2]

TYPES OF HEPATIC DISEASES

HEPATIC CANCER

Cancer that effects the tumors or other cancer cells.[3] Signs and symptoms: Loss of appetite, feeling sick and vomiting, pain or sweeling in abdomen. Pathophyisiology: Liver is a common site of cancer metastasis from other parts of the body due to high flow rate and extensive capillary network. Liver cells become enlarged and mishappen by cancer cells. May lead to hemorrhage and necrosis. Sources **:** Curcumin from tumeric (*Curcuma longa*); it belongs to the family Zingiberaceae, tea polyphenols from green tea (*Camellia sinensis*); it belongs to the family thecea. Mechanism of action**:** Hesperidin regulating mitochondrial pathway and death receptor pathway; triggering the activation of the mitochondrial pathway by increasing the levels of intracellular ROS, ATP, and Ca^{2+}.[4],[5] Conventional treatment: Treatment for curable tumors: Partial hepatectomy, liver transplant, Treatment for incurable tumors: Ablative therapy, radiation therapy, chemotherapy. Prevention: Prevention involves treating susceptible crops to prevent fungal contamination, and handling the foodstuffs in such a way as to prevent contamination during storage. Iron overload in hereditary hemochromatosis can be prevented by repeated venesection.

NON - ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Nonalcoholic fatty liver disease (NAFLD), defined as genetic-environmental-metabolic stress-related disease with a spectrum of liver disorders.[6] Signs and symptom**:** **A**n enlarged liver or spleen, ascites, or swelling in your belly, jaundice, or yellowing of your skin and eyes. Pathophysiology: Environmental and genetic factors challenge homeostasis and lead to several pathological processes: metabolic disorders, oxidative stress, and inflammation. These processes also fortify each other and cause a disbalance, leading to the development of steatosis and NASH. Sources**:** Resveratrol is contained in red grapes, *Fructus Mori*, *Arachis hypogaea* Linn. and *cacao.*, Curcumin responsible for the yellow colour of the plant *Curcuma Longa* L, is extracted from curry and spice. Mechanism of action: Curcumin can reduce alpha-smooth muscle actin a level in the NASH and can reduce the production of reactive oxygen species and tissue inhibitor of metalloproteinases-1 secreting activated hepatic stellate cells.[7] Conventional treatment**:** Seasonal allergies (allergic rhinitis), diabetes, heartburn, skin damage caused by radiation treatment. Prevention: Protecting your liver is one of the best ways to prevent fatty liver and its complications, you can start by taking several steps: Limit or eliminate alcohol from your diet, Eat a healthy, balanced diet, control diabetes if you have developed the condition.

HEPATITITES C VIRUS (HCV)

This long-term disease evolves slowly, often leading to chronicity and potentially to liver failure.[8] Signs and symptoms: Acute: Yellowing of the skin and eyes, tiredness, nausea, muscle aches. Chronic: Loss of appetite, dark urine, clay-colored stool, joint pain, easy bruising or bleeding. Pathophysiology: Locally, inflammatory process causes liver to swell, Bile channels compressed; damage the cell that produces bile, then blood flow to the liver is impart, causing pressure to rise in the portal circulation, systemic effects related to altered metabolic functions performed by the liver and to infections response in viral hepatitis. Sources: Silymarin is extracted from the seeds of milk thistle *Silybum* marianum, ladanein, extracted from *Marrubium peregrinum* L. (*Lamiaceae*), is a flavone. Mechanism of action: Silymarin appears to inhibit HCV infection at least at two different levels: it inhibits HCV replication in cell culture and it also displays anti-inflammatory and immunomodulatory actions that may contribute to its hepatoprotective effects.[9] Conventional treatment: Severe liver disease including fibrosis, cirrhosis and hepatocellular carcinoma, liver cancer, liver transplant. Prevention: Preventing HCV involves limiting exposure to the virus in the first instance.This involves: Avoiding or quitting smoking, maintaining ideal weight, managing co-existing health problems, abstaining from all alcohol.

ALCOHOLIC LIVER DISEASE (ALD)

Alcoholic liver disease is the manifestation of liver due to chronic overconsumption of alcohol sequentially leading to alcoholic fatty liver, alcoholic hepatitis and then to alcoholic cirrhosis.[10],[11] Signs and symptoms : Increased thirst, swelling in the legs and abdomen, darkening or lightening of the skin, dark bowel movement, bleeding gums**.** Pathophysiology: Alcohol is readily absorbed from the stomach, but most is absorbed from the small intestine.

Alcohol dehydrogenase

⇩

Acetyldehyde

⇩

Acetyldehyde dehydrogenase

⇩

Acetate

Sources: Turmeric (*Curcuma longa*), is a perennial rhizomatous herb from the family Zingiberaceae, green tea (*Camellia sinensis*), it belongs to the family thecease. Mechanism of

action: Epigallocatechin-3-gallate (EGCG) affected hepatic iron uptake and inhibited iron absorption in the small intestinal via upregulating hepcidin mRNA levels and transferrin as well as hepatic transferrin receptor protein levels, thus reducing serum and hepatic iron levels.[12] Conventional treatment: Liver transplant, abstinence, medications-stem cell therapy. Prevention: To prevent alcoholic liver disease and other conditions linked to the consumption of alcohol, people are advised to follow national guidelines for limits of alcohol consumption. Green tea is one of the best documented plants that have been used in the prevention of liver diseases.

HEPATIC FIBROSIS

Liver fibrosis is a wound-healing response to hepatic injury.[13] Signs and symptoms: Appetite loss, difficulty thinking clearly, fluid buildup in the legs or stomach, jaundice (where the skin and eyes appear yellow). Pathophysiology: Progressive accumulation of fibrillar extracellular matrix (ECM) in the liver is the consequence of reiterated liver tissue damage due to infective (mostly hepatitis B and C viruses), toxic/drug-induced, metabolic and autoimmune causes, and the relative chronic activation of the wound-healing reaction. Sources: Silymarin is a flavonoid complex consisting of silybin, silydianin and silychrisin and is extracted from the seeds of *Silybum marianum*, ginseng, referred to as the roots of *Panax ginseng.* Mechanism of actions: Quercetin - Inhibition of activated HSCs have been ascribed to upregulation of MMPs and regulating profibrogenic/antifibrogenic molecules balance.[14] Conventional treatment: Cirrhosis, liver failure, portal hypertension, and hepatocellular carcinoma, liver transplantation is the only treatment available for patients with advanced stages of liver fibrosis. Prevention: Clinical experiences have now recognised that the rapidity and completeness of the response to conventional therapy are important factors in preventing hepatic fibrosis.

CONCLUSION

Herbal plants clearly indicate that flavonoid from the plant source have enormous potential for the prevention and treatment of liver diseases. There are eight classes of flavonoids: Anthocyanidins, proanthocyanidins, flavones, flvonols, flavan-3-ol, flavanones, isoflavones, chalcones. In this article we reviewed the scientific merit of the selected herbal flavonoids studied for their hepatoprotective mechanism of actions for hepatic cancer, non-alcoholic fatty liver diseases (NAFLD), hepatitis C virus (HCV), alcoholic liver diseases (ALD) and hepatic fibrosis are more commonly cured by rutin, quercetain, silymarin which comes under

the class of flavonoids by flavonols & flavonone. We have summarised the effect of extracts of herbs of different flavonoids; Silymarin is extracted from the seeds of milk thistle and curcumin is extracted from turmeric which are used for the prevention and treatment of hepatic fibrosis and hepatic liver; compounds of different herbs (example: green tea, citrus seeds of orange) on liver injury changes in the biochemical parameters. Herbal drugs rich in flavonoids, widely existing in plants and plant-based products, have attracted increasing attention as potential agents for prevention and treatment of liver diseases due to their outstanding effects on mediating pathways involved in the pathogenic process. We therefore conclude that herbal flavonoids are the most important sources of hepatoprotective and liver regeneration medicines. Moreover, the combination of the traditional herbal medicines with the modern and conventional medicines may be one of the best option for the treatment of liver diseases and associated disorders.

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- that herbal drugs have an enormous potential for the treatment of liver
- diseases. In this article, we reviewed the scientific merit of selected
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- major hepatoprotective mechanism identified by the majority of the
- studies is through combating the oxidative stress that damages the
- liver. We have summarized the effect of extracts and compounds from
- different herbs on liver injury considering changes in their biochemical
- parameters. We also presented the possible data available in the liter-
- ature for different plants regarding their phytochemical constituents.
- We, therefore, conclude that herbs and herbal preparations are among
- the most important sources of hepatoprotective and liver regeneration
- medicines. However, further research is needed to identify, character-
- ize, and standardize the active ingredients, useful compounds, and
- their preparations for the treatment of liver diseases. Moreover, a
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ACKWOLEDGEMENT

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REFERENCES

1. Manach C, Scalbert A, Morand C, Remesy C, Jimenez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr., 2004; 79(5): 727-747.
2. Xiao J, Kai G, Yamamoto K, Chen X. Advance in dietary polyphenols as α-glucosidases inhibitors: a review on structure-activity relationship aspect. Crit Rev Food Sci Nutr., 2013; 53(8): 818-836.
3. K. H. Lee, M. H. Yeh, S. T. Kao et al., "The inhibitory effect of hesperidin on tumor cell invasiveness occurs via suppression of activator protein 1 and nuclear factor-kappaB in human hepatocellular carcinoma cells," Toxicology Letters, 2010; 194: 1-2, pp. 42–49.
4. M. H. Yeh, S. T. Kao, C. M. Hung, C. J. Liu, K. H. Lee, and C. C. Yeh, "Hesperidin inhibited acetaldehyde-induced matrix metalloproteinase-9 gene expression in human hepatocellular carcinoma cells," Toxicology Letters, 2009; 184(3): 204–210.
5. L. Zeng, W. J. Tang, J. J. Yin, and B. J. Zhou, "Signal transductions and nonalcoholic fatty liver: a mini-review," International Journal of Clinical and Experimental Medicine, 2014; 7(7): 1624–1631.
6. L. Zeng, W. J. Tang, J. J. Yin, and B. J. Zhou, "Signal transductions and nonalcoholic fatty liver: a mini-review," International Journal of Clinical and Experimental Medicine, 2014; 7(7): 1624–1631.
7. Leclercq IA, Farrell GC, Sempoux C, dela Peña A, Horsmans Y. Curcumin inhibits NF-kappaB activation and reduces the severity of experimental steatohepatitis in mice. J Hepatol, 2004; 41: 926–934.
8. The influence of natural products upon drug discovery. *Newman DJ, Cragg GM, Snader KM*; *Nat Prod Rep., 2000 Jun; 17(3): 215-34.*
9. Morishima C., Shuhart M.C., Wang C.C., Paschal D.M., Apodaca M.C., Liu Y., Sloan D.D., Graf T.N., Oberlies N.H., Lee D.Y.W., et al. Silymarin inhibits *in vitro* T-cell

proliferation and cytokine production in hepatitis C virus infection. Gastroenterology, 2010; 138: 671–681.

10. Maher JJ. Exploring alcohol's effects on liver function. Alcohol Health Res World, 1997; 21: 5-12.
11. Singal A, Anand B. Recent trends in the epidemiology of alcoholic liver disease. Clinical Liver Disease, 2013; 2: 53-6.
12. Y. Ren, F. Deng, H. Zhu, W. Wan, J. Ye, and B. Luo, "Effect of epigallocatechin-3-gallate on iron overload in mice with alcoholic liver disease," Molecular Biology Reports, 2011; 38(2): 879–886.
13. S. L. Friedman, "Mechanisms of hepatic fibrogenesis," Gastroenterology, 2008; 134(6): 1655–1669.
14. L. D. Hernández-Ortega, B. E. Alcántar-Díaz, L. A. Ruiz-Corro et al., "Quercetin improves hepatic fibrosis reducing hepatic stellate cells and regulating pro-fibrogenic/anti-fibrogenic molecules balance," Journal of Gastroenterology and Hepatology, 2012; 27(12): 1865–1872.