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Review Article

Hepatoprotective potential of propolis

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ABSTRACT

Propolis is a resinous mixture collected by honey bees from different flowers, buds, fruits, and several other parts of plant. The bees bring it to their hive on their hind legs, just like pollen. They mix it with their own wax and saliva, resulting in the formation of propolis. Propolis has an extremely complex chemical composition that includes flavonoids, phenolic acids, their esters, ketones, alcohols, amino acids, and several other inorganic compounds, making it a good Pharmacologicallyuseful compound for dealing with various hepatic disorders. Propolis protects liver toxicity by reducing the free radicals by its magical Activities compounds. Propolis possess antioxidative, antiulcer, antimicrobial, and antitumor activities induced by several xenobiotics and has shown to be a magical remedy in handling and inhibition of several disorders of liver related to severe clinical stages, from acute liver failure to hepatocellular carcinoma.

1. Introduction

From the ancient time, peoples are enjoying charmed of propolis. The Arabians, Egyptians, and Roman physicians have documented propolis for its various medicinal properties and they have used it for mummifying, protection from wound, as a mouthwash, and several other activities. Moreover, propolis was widely famous for its remedial effects. Healing properties of propolis is mentioned as the "Balm of Gilead" in Holy Bible.[1] Famous Greek philosopher, Aristotle mentioned propolis in his book "Historia Animalium" a substance, that honey bees smeared at their hive entry as a cure for bruises and sores.[2] Roman scholar, Plinius (23–79 A.D.) hypothesized that propolis originates in the buds of trees like willow, poplar, elm, and reed. He also mentioned about use of propolis at that time "current physicians use propolis as a medicine because it's extracts reduces swelling, softens indurations and relieves pain".[3]

Propolis has been widely used to cure several hepatic disorders, including "acute liver failure, alcoholic and non-alcoholic fatty liver diseases, liver fibrosis, liver cirrhosis and liver cancer". In this review a portrait has been made on propolis as a potent hepatoprotective agent to cure liver from acute liver failure to hepatocellular carcinoma.

2. Propolis and its Properties

Propolis is a waxy substance collected by bees from different plant exudates. Plants protects themselves from foreign pathogens by producing several phytochemicals such as phytoalexins, saponins, polyphenols, esters, alcohols, many of which have been extracted and are used in treatment of several diseases and are very good source of antioxidants, vitamins, and several plants based secondary

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metabolites.[1] Plant defence compounds, collected by bees mainly include phenols and terpenoids. Honey bees and other species of social bees identify these properties of plants, collect, and use these plant products to make propolis and further used to protect the colony from virus, bacteria, protozoans, and several other enemies.[4] Bees in colonies that collects propolis are healthier and live longer, comparison to other worker bees that do not collect propolis, and consumption of propolis by bees supplements their immune system to protect them from several pathological challenges.[5]

The compounds present in propolis varies as per the flora of that place from where it is collected, season of collection (as number of plants that flower and their composition of phytochemicals varies according to the season, stress and photoperiodism) as this variability affects the medicinal properties of compounds produced by plants. Standardized propolis products does not vary in their main bioactive composition and is usually regarded as safe, with minimal interaction with pharmaceutical drugs, which is also proven in clinical trials.[6] In current research scenario, propolis has been reported to possesses antioxidant, antibacterial, antiviral, anti-inflammatory,[7] immunomodulatory, hepatoprotective, nephroprotective,[8,9] cardioprotective, antidiabetic and anticancer activity.[10] Historically propolis has been widely used to cure several diseases. Propolis has also been considered over other natural alternatives products because it is generally less expensive, easily available, and rarely causes any side effects and as it is collected from different sources, so it contains various natural products from various medicinal plants.[11,12]

3. Hepatoprotective Activity of Propolis

Liver diseases are a set of pathological conditions which are characterised by the several liver function test markers, normally a healthy adult liver consists of 5 or less than 5% fat content, if this fat content increases in hepatocytes, the person suffers from fatty liver disease or steatosis.[13] If this condition is not treated and further symptoms develops, which shows ballooning of hepatocytes and inflammation in liver cells, however, this condition is also treatable and if not treated these symptoms further develops in to fibrosis[14] which are having three different stages and condition can be reversed but at this point if disease is not treated, condition now develops into cirrhosis which is having no any medicine for treatment, although their few medicines are available which can slowed down the process of cirrhosis but cannot treat completely and the person suffering from this condition have to go for liver transplantation otherwise hepatocellular carcinoma will develop and soon person may die.[15]

4. Propolis and Acute Liver Failure

Acute liver failure is most common clinical manifestation related with liver injury, in which level of liver function test marker enzymes (AST, ALT, ALP, GGT, bilirubin total and bilirubin direct) significantly elevated and causes problem in normal functioning of liver.[16] Propolis is a very good hepatoprotective agent against acute liver failure condition. Propolis increases the tissue glutathione level while stop lipid peroxidation level. Consequently, propolis has been reported to increase antioxidant activity against mercury induced-toxicity by regulating antioxidant enzyme system.[17] Studies also showed that propolis have protective role against CCl_4 induced hepatorenal oxidative stress and resultant injury.[18] Propolis showed hepato-protective activity in liver damage of rats caused by alcohol, CCl_4 and acetaminophen. Banskota et al.[19] isolated several phenolic compounds and diterpenic acids from propolis showing hepatoprotective activity. Bhadauria et al.,[20] have reported multiple treatment of propolis can prevent the level of liver function test marker enzymes towards control if propolis is taken regularly, it can save liver from model hepatotoxicant[21] several other papers have found that propolis prevents liver injury from toxic elements such as aluminium,[22] acetaminophen,[23,24] mercury,[25] and beryllium.[26]

5. Role of Propolis in Drug Induced Toxicity

People suffer with diseases, they take some type of medicines, which are alien to their body. Body assumes these substances as alien and these aliens produce some type of toxicity inside the body either given acutely or chronically.[27] Cancer and tuberculosis are the two most common disease, which uses wide range of medicines. Consuming theses medicines causes several side effects along with toxicity in liver and kidney as they are major organs responsible for the metabolism of these medicines and their reactive metabolites.[28] Cancer is the most prominent health complications of current scenario, ranked as second most common disease in the world, followed by cardiac diseases in several countries in the world.[29] Cancer treatment includes chemotherapy, radiotherapy, surgery, and now immunotherapy. These methods are used in the treatment according to type of cancer and level of severity. Chemotherapy is a method, which is having toxic effects also, especially against multiplying cells, and is performed with natural or synthetic chemicals. The main aim of chemotherapy is to increase patients' life hope and provide further a better life. However, several chemotherapy-related complications and toxic effects are reported depending on the medication used.[30] The common non-hazardous and natural compounds such as propolis is used from the ancient times to cure hepatic abnormalities and is very rich source of antioxidant molecule that protects liver from several

xenobiotics. Propolis is one of the natural compounds that is having a very good source of antioxidant and restores cellular functions by preventing several side effects caused by alien substances to our body. Seven et al.,[31] reported propolis and its nano-formulation against cisplatin induced toxicological manifestations in rats and in their study, they concluded that propolis and its nanoparticles protects liver and kidney by modulating Bcl-2 and Bax levels. Along with chemotherapeutic drugs, antituberculosis drugs also causes several toxic effects in liver and kidney.[32] Treatment of tuberculosis takes six-month course of medicines, including rifampicin, isoniazid, ethambutol, and pyrazinamide, which exerts great side effects on liver and kidney. Sahu et al.,[33] reported protective effects of propolis against antituberculosis drugs (ATDs) resulted hepato-renal toxicities. Administration of ATDs for 8 weeks along with propolis at (100, 200, 400 mg/kg) conjointly in rats and found that increase in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, triglyceride, and cholesterol along with reduction in glucose and albumin level were noted after ATDs induced hepatic injury and recovery was observed in propolis groups, maximum recovery was noted in 400 mg/kg group. Increase in oxidative stress triglyceride, cholesterol and CYP2E1 activity and decrease in antioxidant pool (reduced glutathione, catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, glucose-6-phosphatase dehydrogenase) were observed. Histopathological and electron microscopic observations also revealed their biochemical results indicated hepato-nephro protective potential of propolis whereas, TNF-α, IL-6 and IGF-1 also confirmed therapeutic role of propolis at molecular level in their study. In the conclusion, propolis prevents drug induced toxicity by combating the free radicals and maintaining the level of antioxidant enzymes by preventing free radicals' activity, maintaining the level of CYP2E1 activity, maintaining inflammatory markers level, also confirmed by light microscopy study of tissues and electron microscopy study.

6. Propolis and Fatty Liver Diseases

The term fatty liver diseases (NAFLD) or steatosis describes long-lasting liver abnormalities, characterized by excess accumulation of lipid droplets (steatosis) without excess alcohol intake. Irregular accumulation of fat if becomes >5% in hepatocytes, deprived of any evidence of hepatic injury or hepatic fibrosis is generally termed as simple or bland hepatic steatosis.[34] However, a good number of patients with steatosis develops to an advanced form of the disease termed as Non-alcoholic steatohepatitis (NASH). In NASH, steatosis exists with hepatic injury and inflammation and may trigger further necrosis, fibrosis, and cirrhosis, in addition to develop a risk of liver cancer.[35] The NAFLD is usually more commonly found in persons with central obesity (deposited abdominal fat excessively), type 2 diabetes, hypertension, and dyslipidaemia.[36] Till date, no pharmacological compound has been licensed specifically for the treatment of NAFLD. The recommended medication for NAFLD is mainly focuses on lifestyle changes including proper diet and physical activities. Although biological machineries, which leads the progression of NAFLD has not been completely clarified, but oxidative stress is suggested as a key factor in the development of NASH from NAFLD.[37] As per Kismet et al.,[38] propolis on NAFLD showed protection observed by histopathological, biochemical, and anti-inflammations activities. From their study they confirm that the anti-oxidant and anti-inflammatory properties of propolis prevents the progression of NAFLD to NASH and conclude that further randomised clinical study is needed which can confirms role of propolis in the treatment of NASH and NAFLD.

7. Propolis and Hepatitis

Hepatitis of liver refers as an inflammatory state of liver, which is usually caused by viral infections, but several other possible causes of hepatitis are also reported. These comprise mainly autoimmune hepatitis and hepatitis occurs due to secondary result of medications, drugs, toxins, alcohol, or any xenobiotics induction.[39] Autoimmune hepatitis occurs when our own body cells produce antibodies against our own liver tissues. Excessive consumption of alcohol may results into liver cell damage and inflammation, which is termed as alcoholic hepatitis condition.[40] Alcohol directly injures hepatic cells. With the time progression, it causes permanently damage to hepatic cells and may lead to failure of liver and liver cirrhosis, a thickening and scarring in the hepatic tissues. Apart from alcohol other causes of hepatitis are overdose of medications and exposure to xenobiotics such as acetaminophen, carbon tetra chloride, lipopolysaccharide etc. Hassan et al.,[41] have tested Saudi propolis against CCl_4 induced acute hepatitis and found in their experiment that propolis contains several compounds from gas chromatographic separation results revealed that propolis have forty-one natural compounds. In his result of hepatitis, they found that propolis is a compound that inhibits the elevation of liver function test markers enzymes, level of Malondialdehyde (MDA) which indicates the level of oxidative stress in liver tissues, he also found that propolis restores level of enzymatic activity of Glutathione-S-transferase (GST), Catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GSH) in liver against hepatitis. Mounieb et al.,[42] reported that the propolis treatment against concanavalin A induced hepatitis have shown better protection in oxidative stress (in terms of lipid peroxidation), antioxidant enzymes (such as SOD, CAT etc.) and regulating the level of cytokines (mainly TGF-

β, TNF-α, and IL-6) in hepatitis rats and have resulted in improved level of liver function test markers (AST, ALT, ALP, GGT, Bilirubin). Results of El-Mahalaway et al.,[43] also corelates several other findings related with hepatoprotective activity of propolis as in their experiment they reported lipopolysaccharide and D-galactosamine induced hepatitis and have noted vacuoles necrosis in hepatic cells and damaged hepatocytes histologically as well as immunobiologically in toxicant group but treatment with propolis preserved this cellular structure with its antioxidant activity.

8. Propolis and Liver Fibrosis

During liver fibrosis, excess accumulation of extracellular matrix proteins occurs mainly collagen. Liver fibrosis further develops into cirrhosis, ultimately liver failure which requires liver transplantation.[44] Till date our information towards mechanisms of liver fibrosis has become greatly advanced. Activated stellate cells, portal fibroblasts have been recognized as main collagen-producing cells in the damaged liver. Activation of these cells produces fibrogenic cytokines mainly TGF-β1, leptin and angiotensin-II. Reversibility of hepatic fibrosis in patients have recently been documented in some experiments, which have shown researchers to invent novel antifibrotic drugs.[45] Although several therapeutic interferences have been reported to be effective in experimental models of liver fibrosis but their efficacy in humans is still not well documented.Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. Our knowledge of the cellular and molecular mechanisms of liver fibrosis has greatly advanced. Activated hepatic stellate cells, portal fibroblasts, and myofibroblasts of bone marrow origin have been identified as major collagen-producing cells in the injured liver. These cells are activated by fibrogenic cytokines such as TGF-β1, angiotensin II, and leptin. Reversibility of advanced liver fibrosis in patients has been recently documented, which has stimulated researchers to develop antifibrotic drugs. Emerging antifibrotic therapies are aimed at inhibiting the accumulation of fibrogenic cells and/or preventing the deposition of extracellular matrix proteins. Although many therapeutic interventions are effective in experimental models of liver fibrosis, their efficacy and safety in humans is unknown. This review summarizes recent progress in the study of the pathogenesis and diagnosis of liver fibrosis and discusses current antifibrotic strategies.

Liver fibrosis was earlier believed to be an irreparable machinery due to collapse of hepatic parenchyma and their substitution with the excess collagen tissue but now it is model for wound-healing comeback to chronic liver injuries. However, it got major consideration from 1980s, when hepatic stellate cells (HSCs), recognized as the chief collagen-producing cells.[46] Models for studying mechanism of fibrogenesis in rats and in transgenic mice have been already developed by using several chemicals such as thioacetamide, carbon tetrachloride and so on. Since the demonstration of the reports that even advanced hepatic fibrosis is rescindable, researchers are in continuous discovering antifibrotic therapies with natural origin and without any side effect such as propolis.[47] Inflammation is responsible for the pathogenesis of steatosis and fibrosis.[48] A study performed by Zhao et al.[49] 18 weeks intervention of propolis at 900 mg/kg daily dose significantly reduced TNF-α concentrations, which is a major inflammatory cytokine. A clinical trial disclosed propolis supplementation recovers hepatic steatosis and fibrosis score in patients having NAFLD,[50] involving total of 54 patients with NAFLD and have found that propolis improves liver function test markers, blood glucose level fasting as well as after meal and reduces the level of highly sensitive C-reactive proteins (hsCRP) at 250 mg/kg dose twice in a day for four months. In recent years, Kismet et al.[39] found that propolis intake ameliorates histological score during steatosis, hepatocellular ballooning, and lobular inflammation, which reduces liver function test markers enzymes in rats with non-alcoholic steatohepatitis and hepatic fibrosis additionally, histopathology of liver.[51] Inflammation, oxidative stress also plays a key role in the development of fibrosis through activation of stellate cells.[52] Bhadauria,[20] have reported defensive part of propolis against carbon tetrachloride (CCl_4) induced hepatic fibrosis, in her experiment she has given propolis two weeks at 200mg/kg after induction of fibrosis by CCl_4 treatment of five weeks and reported that treatment with propolis significantly reverses level of transaminases, antioxidant enzymes and oxidative stress level towards control which was also confirmed by histopathological observations. Galangin, a polyphenol present in propolis suppresses inflammation and oxidative stress through activation of nuclear factor erythroid 2 (Nrf-2).[53] Studies have shown that galangin reduces steatosis by promoting autophagy in hepatocytes[54] and prevents HSCs proliferation and collagen gene appearance by constraining TGF-β expression also. A phenolic compound obtained in propolis named caffeic acid phenethyl ester (CAPE), overwhelms translocation of NF-$\kappa\beta$ through IκB degradation or blocking the bindings of NF-κB to genetic materials. Pinocembrin (one more flavonoid present in propolis) has downregulated the appearance of TNF-α, IL-1β, and IL-6 genes. The molecular pathway of the pinocembrin explained that pinocembrin inhibits IκBα, JNK, ERK1/2, and p38MAPK phosphorylation results into inflammatory paths blockage.[55] Other than its anti-inflammatory action pinocembrin also inhibits fibrogenesis by Nrf-2 pathway and halting NF-$\kappa\beta$ and TGF-β1 signalling

mechanism.[56] The medical trials are restricted due to the lack of liver biopsy examination as ethical considerations are not easy. Izzularab et al.,[57] have reported propolis nanoparticles are also having tremendous property to minimise side effects of hepatic fibrosis and nephropathy induced by carbon tetrachloride, in their experiment they found that along with oxidative stress and antioxidant enzymes gene level regulation of TGF-β, nephrin, and Caspase-9 increases drastically, while decrease in Bcl-2 level was reported, treatment of propolis nanoparticles at dose of 200 mg/kg reduces expression of these enzymes towards normal group.

9. Propolis and Cirrhosis

Hepatic cirrhosis is explained as the "progression of regenerative nodules which are surrounded by fibrous bands in response to chronic liver injuries, which leads to portal hypertension and end stage liver diseases".[10] Current developments in understanding of pathophysiology of cirrhosis and complications related with its treatment, results in enhanced management of this disease, quality of life and expectancy of affected people having cirrhosis. But currently, transplantation is solitary option for patients, but several pharmacological therapies that halt the progression to decompensated cirrhosis from compensated cirrhosis or can reverse cirrhosis to its normal state are currently being developed, there are few reports that says that they have reversed hepatic cirrhosis during prophylactic experimentation, but still curative studies are needed to further explored the process of reversal of cirrhosis to normal hepatic architecture.[58] Propolis in several fibrosis processes have been reported to hault and reversal of whole process of conversion of early stages of fibrosis to severe stages, but no any such reports are available currently that explains the role of propolis in cirrhosis. So, in cirrhosis role of propolis is still needs to be explored and its mechanism in pathophysiology of hepatic cirrhosis.

10. Propolis and Hepatocellular Carcinoma

The components of propolis possesses strong activity against several type of tumour cells and stops the process of angiogenesis and helps in cell cycle arrest in tumour cells. Compounds obtained from propolis such as CAPE[59] and artepillin C have been reported to possess anti-tumoral properties.[60] This composition of propolis is involved in cell-cycle arrest, hault of matrix metalloproteinases, anti-angiogenesis consequence and inhibit transfer of cancer cells from their origin to other body parts.[61] Propolis has capability to halt DNA synthesis in cancer cells and the activity to cause aging of tumour cells (programmed cell death) and have the ability to place into action the white blood cells for engendering those molecules which are involved in the regulating the function of B, T, and natural killer cells.[62] Several other compounds which are present in propolis including galangin, cardanol, nemorosone, caffeic acid, gallic acid, benzoic acid, and hespertin are involved to avoid the speedy division of cancer cells.[63] The cytotoxic activity of natural killer cell was found to be increased with the use of propolis for three days against murine lymphoma.[64] The occurrence of tumor suppresser proteins in CAPE results into apoptosis of the C6 glioma cells.[65] Caffeic acid and their esters along with diterpenoids and phenolic compounds has the damaging aptitude towards cancer cells. Propolis anti-tumor effect is due to the polyphenolic constituents combined function present in it.[66] Reduction in the construction of glutathione in tumour cells due to radiations, is subsequently fulfilled by propolis, as the synthesis of glutathione in haematopoietic tissues is maintained by propolis.[67] Badria et al.,[68] have reported cytotoxic activity of propolis against liver, breast, and colorectal cancer and have found that propolis is very effective in treatment of these cancer cells. Turan et al.,[69] have observed the effect of propolis on colon, liver, breast, cervix, and prostate cancer cell line and found that compounds present in propolis acts on preventing the spread of cancer cells and inhibit their growth by encouraging apoptosis in these cancer cells. According to Sameni et al.,[70] propolis extracted in ethanolic solution, was examined for its anti-cancer properties, they counted the aberrant crypt foci (ACF) and the pathological lesions in the distal colonic epithelial tissues, expression of beta-catenin, induced nitric oxide synthase and cyclooxygenase-2 proteins, as these proteins are majorly involved in the incidence and progression of tumour. Administering propolis significantly decreases the number of ACFs and pathological lesions when compared with cancer control groups. The propolis also reduced expression of above-mentioned proteins, responsible for causing and developing cancer.

11. Limitations

In this review, we have discussed only therapeutic role against several hepatic disorders from acute liver failure to hepatocellular carcinoma and have shown good therapeutic activity along with standard medications. Additionally, we focused on different pathological conditions of liver and their possible treatment with propolis. This review will help for proper liver medication in hepatic disorders and help to design potential drugs with propolis as only therapy or with adjuvants with less side effects and high specificity with its related hepatic abnormalities.

12. Conflicts of Interests

The authors have no financial interests or conflicts of interests.

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None.

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