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Effect of Medicinal Plants on Liver and Malaria Pathogenesis

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Abstract

This seminar reviewed the literatures on the effects of medicinal plants on liver and malaria pathogenesis. Malaria parasite has a complex life cycle that takes place both inside the mosquito and human beings. Generally, diagnosis of malaria is classified into clinical and parasitological diagnoses. Lack of clear understanding on the overall biology of Plasmodium (malaria), its life cycle and its mechanism of action has created a challenge in an effort to develop new drugs, and preventive methods against malaria such as using malaria vaccines and vector control. They have been a rise in the use of herbal supplements, natural products, and traditional medicines over the years. The use of herbal plants or their preparations in the management of various diseases including liver diseases has been practiced for several decades and its extension in current dispensation is recognized. It has been shown that the effect of medicinal plants is somehow related to belief, tradition and culture of the community. However, there are growing concerns related to the safety and toxicities of these medicines. These herbal medicines are associated with complications such as liver damage with a high incidence of mortalities and morbidities. Clinical manifestations range from asymptomatic cases with abnormal liver functions tests to sudden and severe liver failure necessitating

liver transplantation. The liver is a very important organ with a lot of functions such as metabolism, detoxification, and storage of nutrients for the host to survive. Standard liver marker enzymes such as ALT, AST, ALP, albumin, globulin are essential when carrying out liver function tests. Medicinal plant components are essential for and can be beneficial or detrimental to the healthy or diseased liver. Medicinal Plants are an essential part of the human diet and comprise various compounds (photochemical) such as alkaloid (pyrrolizidine), kavalactone which are related to liver health. Selected medicinal plants can provide nutritional and medicinal support for liver diseases. At the present, the knowledge of the effects of medicinal plants on the liver is still incomplete. The most urgent task at the present time is to find the best dietary and medicinal plants for liver health in an endless list of candidates globally. This review updates the knowledge about the effects of medicinal plants consumption on the health of the liver, putting particular emphasis on the potential beneficial and harmful impact of medicinal plants on liver function.

Keywords: Medicinal, Plants, Liver, Malaria, Pathogenesis

Introduction

Malaria is a dangerous infectious illness caused by Plasmodium parasites, spread by bites from infected Anopheles mosquitoes (World Health Organization [WHO], 2021). According to WHO (2021), the illness is distinguished by recurring bouts of fever, chills, and symptoms similar to the flu, and may result in serious issues like cerebral malaria, organ failure, and death if not treated. Malaria continues to be a major issue for public health worldwide, having significant effects on illness, death rates, and economic progress, especially in sub-Saharan Africa and certain regions of Asia (WHO, 2021). The World Health Organization (WHO) reported approximately 241 million malaria cases globally in 2020, with Africa experiencing the majority (95%) (WHO, 2021). In the same year, malaria caused around 627,000 deaths worldwide, with children under 5 years old making up 80% of these fatalities (WHO, 2021). Malaria places a significant economic strain, especially in countries where the disease is endemic. The illness may result in lower output, higher medical expenses, and diminished educational achievement, adding to a pattern of poverty and lack of progress (Sachs & Malaney, 2002).

An effort was made to provide basic information on the history, causes, frequency, and occurrence of malaria. It encompasses both traditional and modern views on cell biology,

pathophysiology, diagnosis, and treatment of malaria, as well as insights from Ethiopia. Prior to this, our aim is to outline the latest advancements in drug, vaccine, and control strategies for malaria. Malaria is an age-old illness that dates back to the earliest times in human history. Hippocrates recognized it as a disease in the fourth century BC (Krettli and miller, 2001). In the 1600s, the medicinal properties of Peruvian bark from the Cinchona tree were recognized for treating fever (CDC, 2006). Heinrich Meckel discovered black-brown pigment granules in the blood and spleen of a mentally ill individual in 1847 (David, 2006). The life cycle of the Plasmodium parasite starts in the human body with an initial infection of the liver. Upon entering the host's body through a mosquito bite, the parasites called sporozoites make their way to the liver and infiltrate the liver cells, also known as hepatocytes (Prudêncio et al., 2006). After entering the hepatocytes, the parasites go through a phase known as the pre-erythrocytic or liver stage, in which they reproduce and transform into merozoites (Meis et al., 1983). These merozoites are subsequently discharged into the bloodstream, capable of invading and replicating inside red blood cells, resulting in the symptoms of malaria (Sturm et al., 2006). The Plasmodium sporozoites possess unique methods for identifying and entering hepatocytes. This process includes the communication between the surface proteins of the parasite and the receptors on the cells of the host liver (Carrolo et al., 2003; Prudêncio et al., 2006). After entering the hepatocytes, the parasites go through a sophisticated developmental process, making use of the host cell's materials to aid in their own increase and reproduction (Meis et al., 1983; Sturm et al., 2006). The parasite's ability to start a productive infection in the human host depends on the successful completion of the liver stage.

Malaria infection can result in different types of liver damage, including mild inflammation and severe, possibly life-threatening conditions like acute liver failure (Anand et al., 2014; Kochar et al., 2010). Liver malfunction may hinder the liver's capacity to carry out important functions like metabolism, detoxification, and protein synthesis, thereby worsening the disease's overall seriousness (Anand et al., 2014; Kochar et al., 2010). Severe liver damage may also result in problems like coagulopathy and hypoglycemia, which can worsen the symptoms of malaria according to Anand et al. (2014) and Kochar et al. (2010). The liver is important in metabolizing and eliminating antimalarial drugs, some of which can harm the liver (Mehta et al., 2013; Gupta et al., 2018). Liver dysfunction can change how these drugs work in the body, which can impact how well they work and increase the chances of negative effects from the drugs (Mehta et al., 2013; Gupta et al., 2018).

Comprehending the liver's function in metabolizing antimalarial drugs is crucial for effectively managing and preventing drug-induced liver damage in individuals with malaria. For many years, different populations across the globe have depended on traditional medicinal plants for the prevention and treatment of malaria. These plants are commonly employed in traditional medicine, frequently as components of holistic strategies for disease management (Kaur et al., 2009; Willcox & Bodeker, 2004). Numerous traditional remedies have undergone scientific research, which has resulted in the discovery of active compounds and how they work against the Plasmodium parasite.Numerous studies have demonstrated the in vitro and in vivo antimalarial activities of various medicinal plant extracts and their isolated compounds (Kaur et al., 2009; Willcox & Bodeker, 2004; Willcox, 2011). These studies have highlighted the potential of medicinal plants to inhibit the different stages of the Plasmodium life cycle, including the liver stage, blood stage, and transmission-blocking activities (Kaur et al., 2009; Willcox, 2011). The mechanisms of action often involve the disruption of parasite metabolism, inhibition of enzymes, and modulation of the host's immune response.

Medicinal plants are believed to have antimalarial effects because of compounds like alkaloids, terpenoids, flavonoids, and quinones, which can work in various ways (Kaur et al., 2009; Willcox, 2011). These substances might show direct anti-parasitic impacts, along with properties that can improve the host's reaction to the infection, such as immunomodulatory and anti-inflammatory effects (Kaur et al., 2009; Willcox, 2011). Furthermore, research has investigated the possible combined effects of medicinal plant extracts or compounds with traditional antimalarial drugs to address drug resistance and enhance treatment results (Kaur et al., 2009; Willcox & Bodeker, 2004). Although many laboratory and animal studies have shown the possibility of using medicinal plants for treating malaria, further testing through clinical trials is necessary to determine their safety, effectiveness, and suitability as complementary treatments (Willcox, 2011). Regulatory frameworks and quality control measures play a vital role in ensuring the standardization and quality of medicinal plant-based products utilized in treating malaria (Willcox & Bodeker, 2004).

Life Cycle of Plasmodium

Plasmodium alternates between vertebrate and mosquito hosts, with its sexual phase in the mosquito.

The transmissive form

The female mosquito injects the sporozoite into the vertebrate's skin along with anticoagulant saliva before feeding on blood. Sporozoites travel through the bloodstream or lymphatic system to infect the liver (in mammals) or the spleen, endothelial cells, and macrophages (in birds and lizards). They enter cells and multiply to create many harmful merozoites (the stage before entering red blood cells). These are discharged into the bloodstream and infiltrate red blood cells. The parasite consumes its host cell within a red blood cell, then reproduces to create additional merozoites that leave and infiltrate fresh red blood cells, a process that is repeated numerous times (the asexual blood cycle, Figure 1) to significantly increase in numbers. The duration from invasion to departure differs among species, 48 hours for Plasmodium Falciparum and Plasmodium Vivax and 72 hours for Plasmodium malariae and Plasmodium ovale, where the simultaneous release of merozoites aligns with fever spikes. Ultimately, the parasite undergoes a sexual phase in which it develops into either a female gametocyte (macro-gametocyte) or a male gametocyte (microgametocyte) inside the host cell. The continuation of the life cycle relies on gametocytes being ingested by a feeding female mosquito's gut, where both types of gametocytes are released from their host cells. Male gametocytes quickly divide into several mobile, flagellated micro-gametes that have the ability to fertilize a female macrogamete and create a zygote (figure 1). The parasite transforms into a moving ookinete, entering the wall of the mosquito's gut and forming a spherical oocyst. The parasite reproduces without the need for a partner to create numerous motile sporozoites within it (sporogony). Mature sporozoites exit the oocyst wall and enter the insect's haemocoel before moving on to the salivary glands. They then penetrate the gland walls to access the mosquito's saliva, preparing for transmission to a vertebrate during another blood meal.

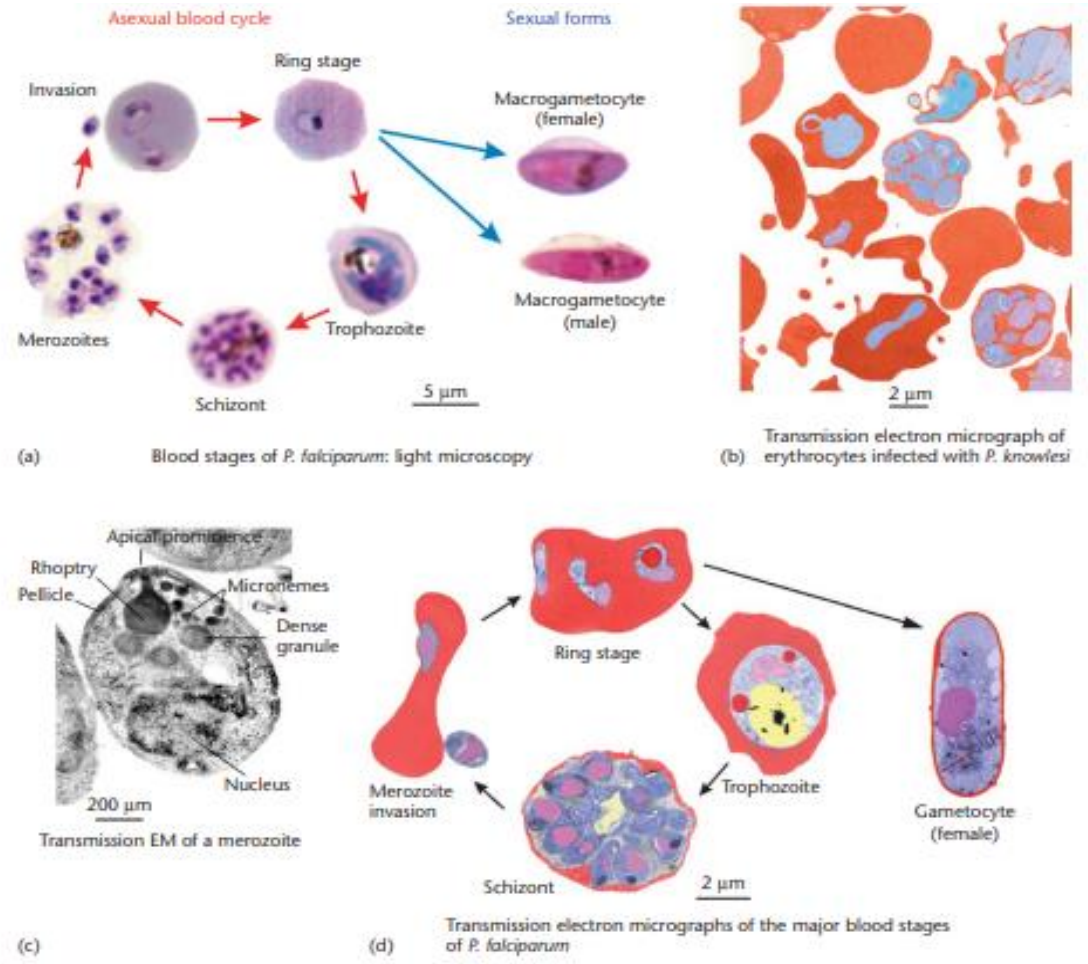

Figure 1: The stages of Plasmodium falciparum in the blood. **(a)** Light micrographs of infected erythrocytes stained as a blood film with Giemsa's stain are assembled into the major stages of asexual blood cycle and the sexual blood stages**. (b)** A transmission electron micrograph of a section through a blood sample infected with the simian malaria parasite Plasmodium knowlesi. A number of different stages are visible. To aid interpretation, false colour has been added to the monochrome micrographs, the parasites being coloured blue and the erythrocytes red. The same convention is followed in most other figures in this article**. (c)** An electron micrograph (EM) of a malaria merozoite, showing its main structural features**. (d)** Electron micrographs of the main blood stages of Plasmodium falciparum are assembled, coloured as in (b); nuclei are indicated in purple. Light micrographs of cells shown in (a) were provided by Gabriele Margos, Bath University, UK.

Medicinal Plants

Medicinal plants are plants that possess healing properties or beneficial pharmacological effects on the human body. Secondary metabolites such as alkaloids, sterols, terpenes, flavonoids, saponins, and glycosides are among the various compounds that medicinal plants naturally synthesize and store. Chemicals found in cyanogenic plants. Quinines, essential oils, resins, lactones, tannins, and other substances. Medicinal plants have been used since ancient times for healing various ailments and diseases. Hieroglyphics on papyrus from Egypt and ancient Chinese texts both mention the healing effects of plants. Indigenous cultures such as African and Native American developed herbal therapies in traditional medical systems like Ayurveda and Traditional Chinese Medicine. Recently, according to the World Health Organization (WHO), a large percentage of people globally depend on herbal remedies for part of their primary healthcare needs. Scientists have found that individuals from various regions worldwide generally use identical or comparable plant species. Approximately 70% of German physicians recommend herbal remedies that can be easily found in Germany. The use of herbal medicine has risen in the United States in the last two decades due to dissatisfaction with costly prescription drugs and a preference for natural or organic remedies. The global need for medicinal plants has increased over the last thirty years. The importance of medicinal plants in tackling health problems, as well as their ability to effectively and safely treat a range of illnesses, is now widely recognized. Due to this heightened awareness, the international trade of medicinal plants is expanding rapidly, often to the detriment of the original populations and natural environments in their home countries (Isaac, et al., 2020).

Medicinal Plants with Anti-Malarial Properties

Numerous studies have investigated the anti-malarial potential of various medicinal plants, focusing on their ability to disrupt the pathogenesis of Plasmodium parasites. Here are some examples of medicinal plants with demonstrated effects on malaria pathogenesis:

Artemisia annua (Qinghaosu)

Artemisia annua, also called Qinghaosu, is a Chinese herbal plant with a long history of being utilized as a remedy for malaria (Tu, 2011).

Artemisinin, the active ingredient, has been thoroughly researched and is commonly used as a very successful treatment for malaria (WHO, 2015).

Artemisinin has been proven to interfere with the life cycle of Plasmodium parasites, specifically in the asexual blood stage, and to prevent the emergence of drug-resistant strains (Meshnick, 2002).

Cryptolepis sanguinolenta

Cryptolepis sanguinolenta, an indigenous plant of West Africa, has been traditionally employed in the treatment of malaria and other fever-related ailments (Adekunle & Aderogba, 2009).

Compounds like cryptolepine in the plant have shown strong anti-malarial effects by disrupting the growth and development of Plasmodium parasites (Onyeibor et al., 2005). Research conducted in 2005 demonstrates that Cryptolepine can hinder the parasite's capacity to break down hemoglobin, which is essential for its existence.

Azadirachta indica (Neem)

The neem tree, also called Azadirachta indica, is a plant with medicinal properties that has been used in different countries, such as India, to heal illnesses like malaria (Biswas et al., 2002).

Research has examined neem extracts and their active ingredient, azadirachtin, for their anti-malarial effects, showing the ability to hinder the growth and progression of Plasmodium parasites (Udeinya et al., 1993).

Neem compounds have been discovered to disturb the parasite's cell membrane, disrupt its metabolism, and hinder its capability to enter host cells (Udeinya et al., 1993).

Cinchona spp. (Quinine)

The bark of Cinchona spp. trees, commonly known as the cinchona tree, has been used for centuries as a traditional treatment for malaria (Achan et al., 2011).

Quinine, the main ingredient, was the first effective treatment for malaria and has been widely used in treating the disease (Achan et al., 2011).

Quinine disrupts the parasite's capacity to detoxify heme, a result of hemoglobin breakdown, causing the buildup of harmful substances that eventually result in the parasite's death (Achan et al., 2011).

Source: Britannica.com, Acessed in August 2024.

Medicinal Plant-Mediated Regulation of Inflammatory Pathways in Malaria

Inflammation is a key component of the host's immune response to Plasmodium infection, but prolonged or excessive inflammation can contribute to the development of severe malaria complications (Gonçalves et al., 2012). Several medicinal plants have been studied for their ability to regulate inflammatory processes in the context of malaria pathogenesis.

Curcuma longa (Turmeric)

According to Gupta et al. (2013), curcumin, found in turmeric, has strong anti-inflammatory properties.

Research has proven that curcumin can block the generation of pro-inflammatory cytokines, like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), when exposed to Plasmodium infection (Reddy et al., 2005).

Reddy et al. (2005) discovered that curcumin can also inhibit the activation of nuclear factor-kappa B (NF-ϰB), an important transcription factor that plays a role in controlling inflammatory pathways.

Carica papaya (Papaya)

Research has been conducted on the anti-inflammatory properties of Carica papaya leaves and fruits in relation to malaria (Rohini & Arunachalam, 2012).

Papaya extracts have demonstrated the ability to prevent the production of pro-inflammatory cytokines, like TNF-α and interferon-gamma (IFN-γ), in Plasmodium-infected cells (Rohini & Arunachalam, 2012).

The ability of papaya extracts to regulate inflammatory mediators such as COX-2 and iNOS is believed to be the reason behind their anti-inflammatory effects (Rohini & Arunachalam, 2012).

Medicinal Plants Targeting Oxidative Stress

Oxidative stress is a hallmark of malaria pathogenesis, contributing to the development of complications and disease severity (Becker et al., 2004). Medicinal plants with antioxidant properties have been explored for their potential to alleviate oxidative stress and mitigate the pathogenic effects of Plasmodium infection.

Moringa oleifera (Drumstick Tree)

Moringa oleifera is a medicinal plant known for its rich antioxidant content, including vitamins, carotenoids, and polyphenols (Saini et al., 2016).

Studies have shown that Moringa oleifera extracts can effectively scavenge free radicals and reduce oxidative stress in Plasmodium-infected cells (Atkinson et al., 2012).

The antioxidant properties of Moringa oleifera have been associated with its ability to protect against Plasmodium-induced oxidative damage and improve overall antioxidant status in the host (Atkinson et al., 2012).

Vernonia amygdalina (Bitter Leaf)

Vernonia amygdalina is a medicinal plant traditionally used in Africa to treat malaria and other ailments (Arawwawala et al., 2010).

Extracts from Vernonia amygdalina have been found to possess potent antioxidant activities, which may contribute to their anti-malarial effects (Arawwawala et al., 2010).

The antioxidant compounds in Vernonia amygdalina, such as flavonoids and terpenoids, have been shown to reduce oxidative stress and protect against Plasmodium-induced cellular damage (Arawwawala et al., 2010).

Medicinal Plants Targeting Cytokine Production

Dysregulated cytokine production is another key feature of malaria pathogenesis, leading to the development of severe complications (Gonçalves et al., 2012). Medicinal plants with the ability to modulate cytokine signaling have been investigated for their potential to mitigate the pathogenic effects of Plasmodium infection.

Artemisia annua (Qinghaosu)

Artemisinin, the active compound in Artemisia annua, has been found to suppress the production of pro-inflammatory cytokines, such as TNF-α and IL-6, in Plasmodium-infected cells (Messori et al., 2016).

Artemisinin's ability to regulate cytokine production may contribute to its anti-malarial properties, as it can help reduce the harmful effects of excessive inflammation (Messori et al., 2016).

Andrographis paniculata (Kalmegh)

Andrographis paniculata is a medicinal plant used in traditional medicine to treat various ailments, including malaria (Mishra et al., 2009).

Studies have shown that extracts from Andrographis paniculata can modulate the production of cytokines, such as IL-6 and IFN-γ, in response to Plasmodium infection (Mishra et al., 2009).

The ability of Andrographis paniculata to regulate cytokine signaling may contribute to its anti-malarial properties and its potential to mitigate the pathogenic effects of Plasmodium infection (Mishra et al., 2009).

Antioxidant Potentials of Medicinal Plants

The complete botanical components of Tinospora cordifolia, Rosmarinus officinalis L., Pleurotus pulmonarius, Humulus japonicas, Cochlospermum angolensis, Picrorhiza kurroa Royle, Ficusp seudopalma Blanco, Aegle marmelos Correa, Berberis vulgaris, Caesalpinia

bonducella, and Artemisia annua L. demonstrated antioxidant effects on liver cancer cells in a dose-dependent fashion, as illustrated in Table 1. Tinospora cordifolia is able to boost levels of antioxidant enzymes (SOD, CAT, GPx) and the nonenzymatic antioxidant GSH, while also decreasing the LPO enzyme (Jayaprakash, et al., 2015). The lipid peroxidation (LPO) and xanthine oxidase (XO) were reduced by Aegle marmelos C. at 25 and 50 mg/kg doses administered orally to mice. Berberis vulgaris and Caesalpinia bonducella enhance GPx and SOD activities, decrease NO levels, and lower lipid peroxidation while boosting non enzymatic antioxidant (GSH) levels and antioxidant enzymes (SOD and CAT) levels as well. Artemisia annua L. was also found to decrease lipid peroxidation and DNA damage, as reported by Addolorato, et al. in 2013. Moreover, Kleinhovia hospital and Morinda pubescens leaves showed 84% and 58.40% DPPH radical scavenging activity, respectively, as reported by Arung et al. (2009) and Kumar and Santhi (2012) using the DPPH radical scavenging method. The outer covering of Terminalia arjuna, Urtica dioica L., and Symplocos racemosa can boost GSH, CAT, and SOD levels, while reducing LPO through GPx (Verma and Vinayak, 2009; Yener, et al., 2009; Prasad, et al., 2010). Semecarpus anacardium boosts glutathione levels in male wistar albino lab rats at a concentration of 200mg/kg. The fruits of C. lansium (Lour.) enhance the scavenging activity of DPPH radical and superoxide anion (Prasad, et al., 2010).

Plant	Compounds	Plantparts	IC_{50}/ dose concentration	Proposed mechanism	Test system
Tinospora cordifolia	Jatrorrhizine, Saponarin, Galactoarabinan	Whole plant	300 mg/kg	Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.	Male wister albino rats.
Kleinhovia hospita	Eleutherol	Leaves	IC50 = 491.8 lM	Scavenged the radical	DPPH radical scavenging method
Morinda pubescens	Hyoscyamine	Leaves	IC_{50} = 289.33±62.14 µg/mL.	58.40% DPPH radical scavenging	DPPH method using L-Ascorbic acid
Terminalia arjuna	Terminoside A	Bark	400 mg/kg	Increase SOD, CAT, GPx and GSH level and reduce LPO enzyme.	Male wistar albino rats
Rosmarinus officinalis L	Rosmanol, Carnosol	Whole plant	0 to 120 g/mL	50% increased antioxidant activity.	Human liver carcinoma HepG2 cells
Pleurotus pulmonarius	Ergosta-5, 7, 22-trien-3β-ol		0.25 mg/ml to 4 mg/ml	DPPH scavenging activity	Mice
Humulus japonicus	Luteolin-8-*C*-glucoside		0.1-2 mg/ml	DPPH radical and hydroxyl radical scavenging activities of methanol extracts of Humulus japonicus were 60% and 35%, respectively	DPPH radical scavenging method
Semecarpus anacardium	Anacardoside, Galluflavanone	Nut	200 mg/kg	Increase glutathione	Male wistar albino laboratory rats
Cochlospermum angolensis	Gallic acid, Protocatechuic acid	Whole plant	$EC_{50} \leq 170$ µg/mL	Increase DPPH scavenging activity	Human liver carcinoma HepG2 cells
Picrorhiza kurroa	Picrorhiza acid		2 µg/mL	Radical scavenging assays (DPPH• and •OH), ferric reducing antioxidant property (FRAP) and thiobarbituric acid (TBA) assay for testing inhibition of lipid peroxidation	Hep3B (human hepatocellular carcinoma)
Ficus pseudopalma Blanco	Lupeol		DPPH (IC50=331.76 µg/mL), nitric oxide (IC50=19.81 µg/mL) and	DPPH, nitric oxide, and FRAP scavenging activity	Hepatocellular Carcinoma (HepG2) cells

Table 1: showing medicinal plants with anti- oxidant activities.

Potential of Phytochemicals

Numerous phytochemicals have been discovered to possess potential against hepatocarcinoma. Figure 3 displays the structures of certain phytochemicals. Curcumin was discovered to cause damage to both mitochondrial and nuclear DNA (Cao, et al., 2007). Previously, DNA damage was identified by the comet assay, which revealed single strand breaks in the DNA molecules. It was also discovered from those studies that the mitochondrial DNA suffered more damage compared to the nuclear DNA. Thus, curcumin leads to an increase in hepatoma cells (Kaur, et al., 2018). Additionally, a plant-derived alkaloid called berberine has been employed in the past to protect plasmid DNA by inhibiting the harmful effects of H2O2 (Choi, et al., 2001). This single phytochemical (Khan, et al., 2010) also causes DNA damage in promyelocytic cancer cells (HL-60). Berberine also induced cell cycle arrest and apoptosis in cancer cells, as shown in the study by Kaur et al. (2018).

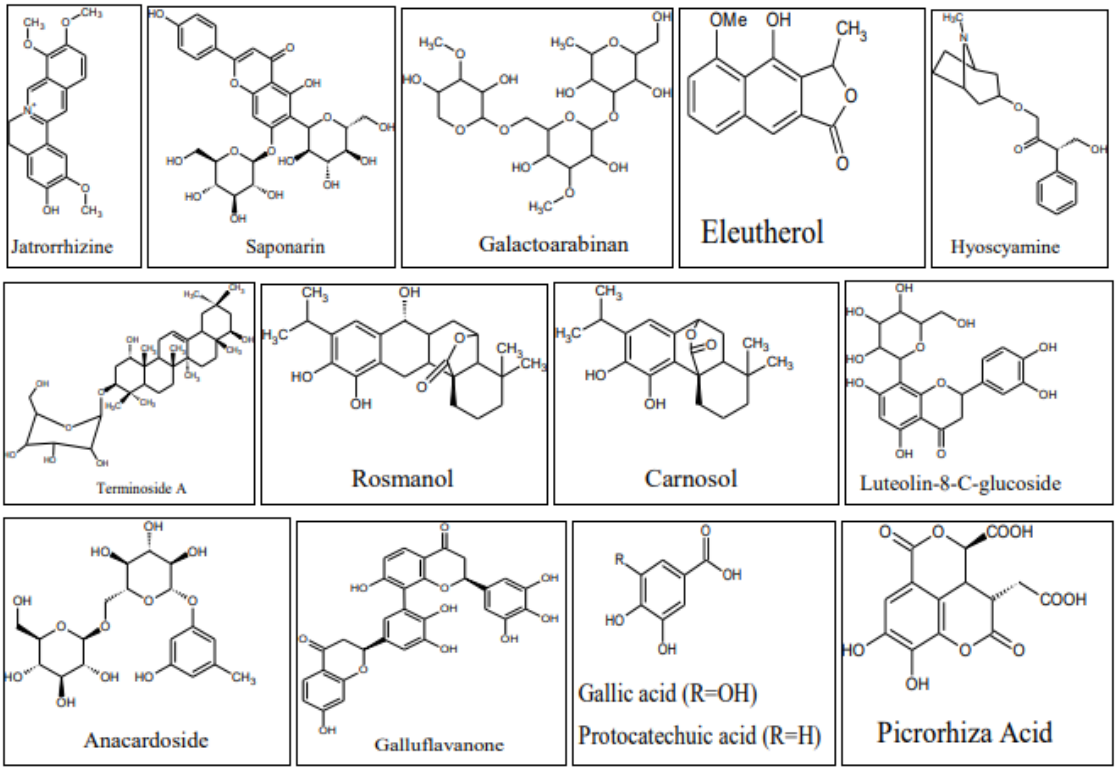

Figure 3: Structures of different phytocompounds

Hepatotoxic Medicinal Plants

Kava-Induced Liver Injury

Teschke and Schulze (2010) performed an extensive examination on the possible liver-damaging effects of kava. They analyzed 26 documented instances of liver damage caused by kava and discovered that most cases were acute hepatitis, some resulting in liver failure and requiring transplantation. The authors determined that extended use of kava extract might lead to serious liver damage.

Teschke et al. (2008) conducted a clinical investigation and in-depth examination of 26 supposed instances of kava-induced liver damage. It was discovered that liver damage from kava usually occurs suddenly, with a delay of 1-3 months. The authors stressed the importance of closely monitoring kava usage and promptly stopping if any signs of liver problems appear.

Green Tea Extract-Induced Liver Injury

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Pyrrolizidine Alkaloid-Containing Herbs and Liver Injury

Stegelmeier et al. (1999) examined the toxicology of pyrrolizidine alkaloids present in different medicinal plants. They stated that these substances have the potential to induce hepatic veno-occlusive disease, resulting in liver cirrhosis and failure. The authors stressed the importance of refraining from consuming herbs that contain pyrrolizidine alkaloids.

Stickel and Shouval (2015) also talked about the liver toxicity caused by pyrrolizidine alkaloid-containing herbs, stating that these substances can lead to acute, subacute, and chronic liver damage.

Aristolochic Acid-Containing Herbs and Nephrotoxicity/Hepatotoxicity

Debelle et al. (2008) examined the worldwide issue of aristolochic acid nephropathy, a serious type of kidney damage linked to the consumption of herbs containing aristolochic acid. They also pointed out that aristolochic acid can lead to liver damage, along with the already well-known kidney damage.

Stickel and Shouval (2015) elaborated more on the liver-damaging properties of aristolochic acid-containing herbs, emphasizing the importance of stringent regulations and steering clear of these herbal products.

Mechanism of Action of Medicinal Plants Induced Liver Toxicity

Oxidative stress

Many hepatotoxic plants contain compounds that can increase the production of reactive oxygen species (ROS) or deplete antioxidant defenses in the liver (Ruan et al., 2014; Xiao et al., 2018).

ROS can damage cellular macromolecules, leading to oxidative stress and inflammation, which can trigger apoptosis or necrosis of hepatocytes (Ruan et al., 2014; Xiao et al., 2018).

Examples: Pyrrolizidine alkaloids, found in plants like comfrey, Senecio and Crotalaria species, can increase ROS production and induce oxidative stress, leading to hepatic necrosis (Ruan et al., 2014; Xiao et al., 2018).

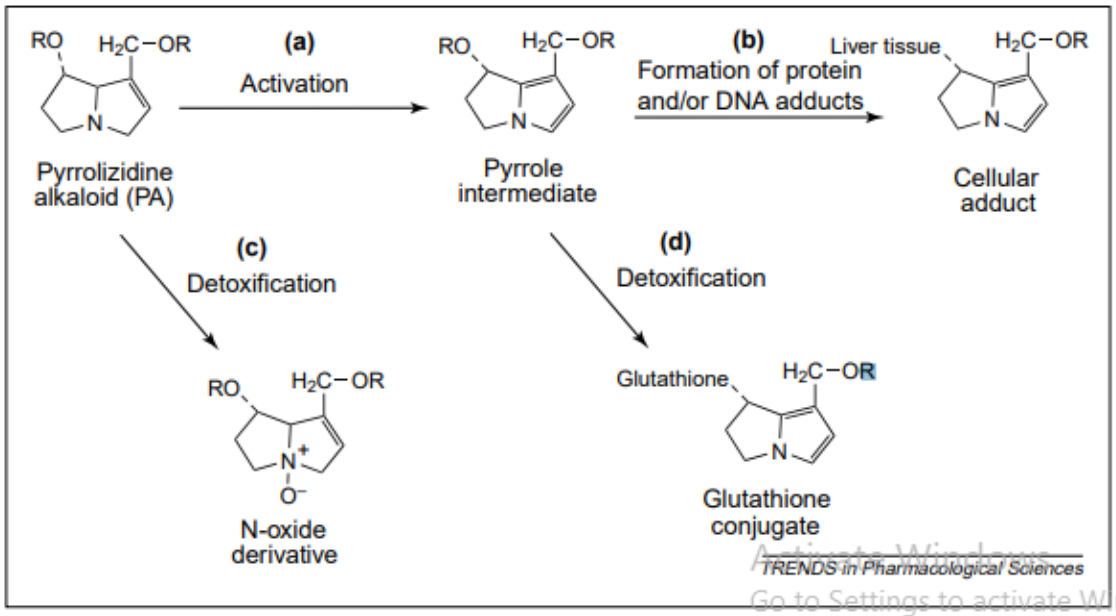


Figure 9: Activation and detoxification of pyrrolizidine alkaloids (PAs). Pyrrolizidine alkaloids are (a) dehydrogenated to produce a pyrrole intermediate, which then (b) reacts with protein or DNA to form a cellular adduct. Alternatively, detoxification occurs when the PA undergoes (c) N-oxidation or (d) the pyrrole is conjugated with glutathione (Dorena, 2002).

Mitochondrial dysfunction

Certain plant-derived compounds can interfere with mitochondrial function, impairing energy production and disrupting cellular homeostasis (Fürst and Zündor, 2014; Barchini and Solinas, 2019)

This can lead to the opening of the mitochondrial permeability transition pore, triggering hepatocyte apoptosis, and also disrupt bile acid metabolism and transport, leading to cholestasis (Fürst and Zündor, 2014; Barchini and Solinas, 2019)

Examples: Microcystins from cyanobacteria (blue-green algae) can inhibit mitochondrial respiration and induce hepatocyte apoptosis (Fürst and Zündor, 2014; Barchini and Solinas, 2019)

Immune-mediated responses

Some plant compounds or their metabolites can act as haptens, triggering an immune response and causing immune-mediated liver injury (Navarro and Seeff, 2013; Stickel and Shouval, 2015).

This can lead to inflammation, infiltration of immune cells, and ultimately, hepatocyte death (Navarro and Seeff, 2013; Stickel and Shouval, 2015).

Examples: Kava, a plant used for its sedative and anxiolytic properties, has been associated with immune-mediated hepatitis in some cases (Navarro and Seeff, 2013; Stickel and Shouval, 2015).

Biliary excretion and cholestasis

Some plant-derived compounds or their metabolites can impair bile flow or bile acid secretion, leading to cholestasis and hepatocyte damage (Teschke and Schwarzenboeck, 2009; Teschke and Eickoff, 2015).

Examples: Germander, a plant used in traditional medicine, has been linked to cholestatic liver injury due to its active constituents (Teschke and Schwarzenboeck, 2009; Teschke and Eickoff, 2015).

Hepatoprotective Medicinal Plants

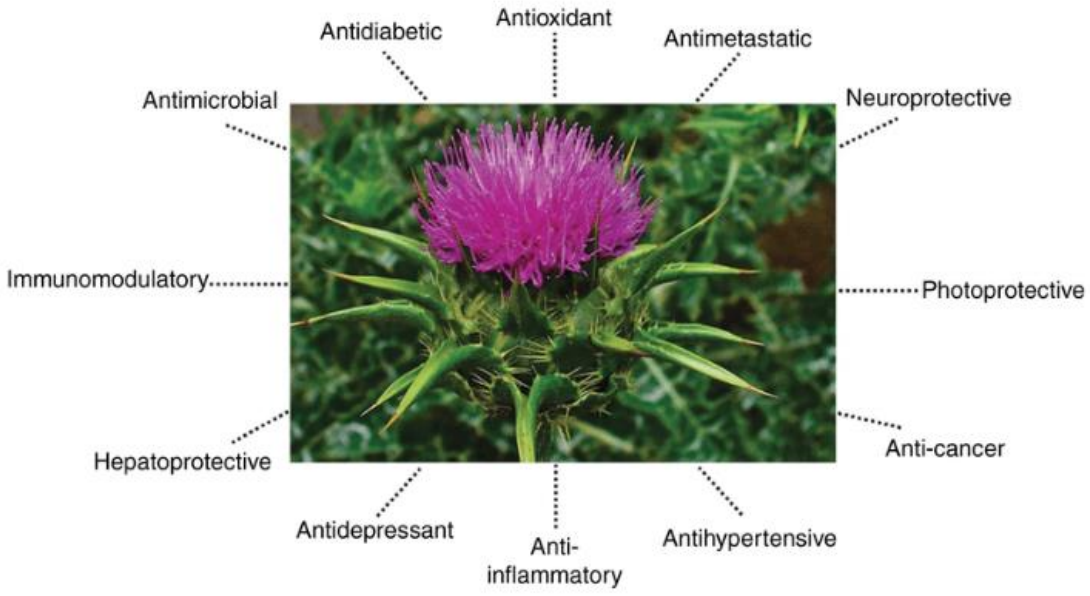
Liver disease is a significant global health concern, with various etiologies, including viral infections, alcohol abuse, and drug-induced toxicity. In recent years, there has been an increasing interest in exploring the potential of medicinal plants as hepatoprotective agents, which can help protect the liver or mitigate liver damage.

Silymarin from Milk Thistle (Silybum marianum)

Silymarin, the active compound extracted from the seeds of milk thistle, is one of the most extensively studied hepatoprotective agents. Numerous studies have demonstrated its ability to protect the liver against various forms of injury.

A systematic review and meta-analysis by Saller et al. (2001) evaluated the efficacy of silymarin in the treatment of alcoholic and/or hepatitis B or C virus-induced liver diseases. The authors concluded that silymarin had a beneficial effect on liver function tests and was well-tolerated.

In a randomized, double-blind, placebo-controlled trial, Lucena et al. (2002) found that silymarin significantly improved liver enzyme levels and reduced the progression of fibrosis in patients with alcoholic cirrhosis.



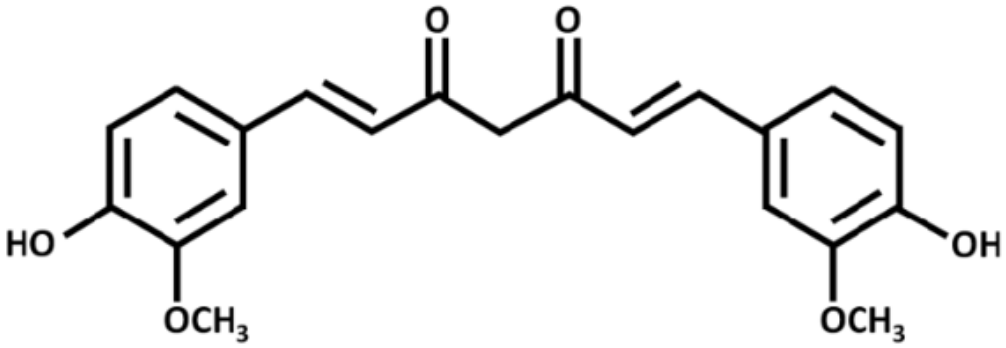
Source: Pixabay.com Acessed in August 2024.

Curcumin from Turmeric (Curcuma longa)

Curcumin, the active compound in turmeric, has been shown to possess potent antioxidant and anti-inflammatory properties, which contribute to its hepatoprotective effects.

Ramirez-Tortosa et al. (1999) demonstrated that curcumin could significantly reduce liver damage and improve antioxidant status in rats with experimentally induced liver fibrosis.

In a clinical study, Shapiro et al. (2006) found that curcumin supplementation improved liver function tests and reduced oxidative stress in patients with nonalcoholic fatty liver disease.



Chemical structure of curcumin, a polyphenolic constituent of turmeric with antioxidant, anti-inflammatory, and anti ulcer effects. Curcumin is a beta-diketone compound containing two substituted aromatic ring held by a seven-carbon chain. Each aromatic ring has one hydroxyl and one one methoxy group.

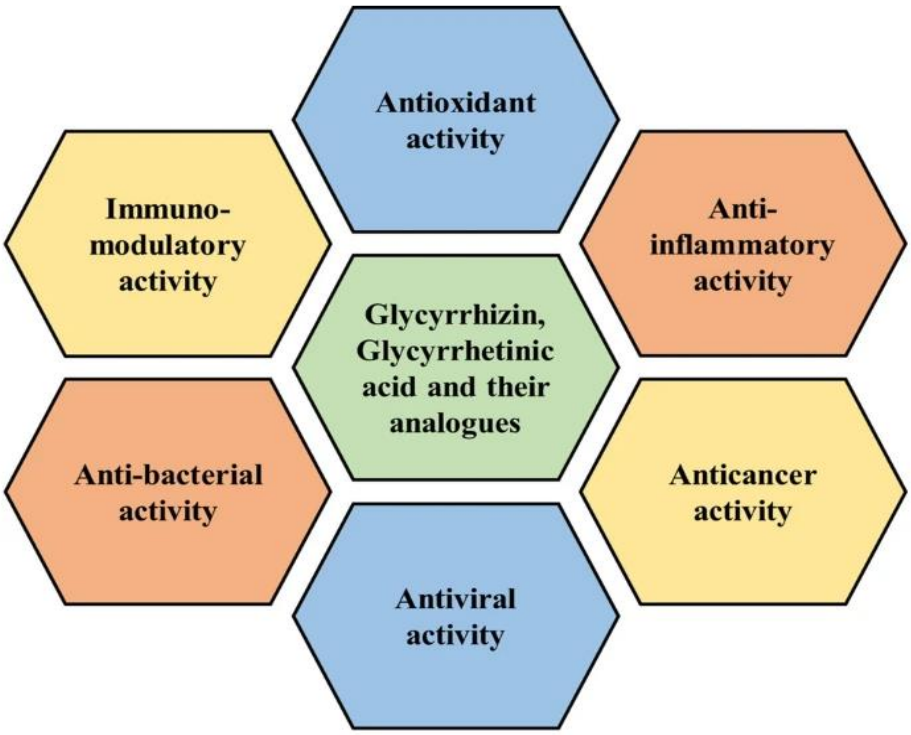
Source: Zhai et al., 2020

Glycyrrhizin from Licorice (Glycyrrhiza glabra)

Glycyrrhizin, a compound extracted from licorice root, has been studied for its hepatoprotective effects, particularly in the context of chronic viral hepatitis.

Ploeger et al. (2001) reviewed the available evidence on the use of glycyrrhizin in the treatment of chronic hepatitis C. They concluded that glycyrrhizin had a beneficial effect on liver function and disease progression.

Arase et al. (1997) conducted a randomized, controlled trial that showed glycyrrhizin administration significantly improved liver enzyme levels and reduced the incidence of hepatocellular carcinoma in patients with chronic hepatitis C.



Source: Mittal 2023

Andrographis paniculata

Andrographis paniculata, also known as "king of bitters," is an herb that has been traditionally used in Ayurvedic and traditional Chinese medicine for its hepatoprotective properties.

Trivedi and Rawal (2001) investigated the hepatoprotective effects of Andrographis paniculata in a rat model of paracetamol-induced liver injury. They found that the herb significantly reduced liver enzyme levels and improved histological parameters.

Handa and Sharma (1990) reviewed the available literature on the hepatoprotective effects of Andrographis paniculata and concluded that the herb possessed potent liver-protecting activities against various hepatotoxins.

Source: indiaMART

Conclusion

Investigating the effects of medicinal plants on liver function and malaria pathogenesis reveals interplay between botanical agents and physiological processes.

Medicinal plants have been studied for their bioactive compounds, showcasing diverse pharmacological properties. Their impact on liver health is of particular interest, considering the liver's pivotal role in drug metabolism and clearance. Additionally, in the context of malaria, a vector-borne disease caused by Plasmodium parasites, the liver serves as a crucial site for the initial stages of infection.

Understanding how medicinal plants modulate liver responses to malaria holds promise for the development of novel therapeutics. As research progresses, unraveling the molecular mechanisms underpinning these effects will contribute not only to malaria management but also to broader insights into hepatic physiology and the pharmacological potential of natural compounds.

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