Jurnal Ilmiah Farmako Bahari
Journal Homepage : https://journal.uniga.ac.id/index.php/JFB

EFFICACY AND SAFETY OF HERBAL MEDICINES IN ASIA

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ARTICLE HISTORY
Received: 24 June 2021 | Revised: 23 July 2021 | Accepted: 26 July 2021

Abstract
Herbal medicine (HM) is a part of future alternative health care. According to the World Health Organization (WHO), almost 70-80% of the population of developing countries rely on HM as an immediate need for health services, one of which is the Asian region. With the high trend of a healthy lifestyle using natural ingredients, drug safety must be a significant concern. This review article aims to provide information on studying the toxicity of Asian herbal plants to hepatotoxic and nephrotoxic activities. The research method was conducted by searching using the keywords “Herbal Medicine(HM),” “Efficacy,” “Nephrotoxicity,” “Hepatotoxicity,” “Asia,” “extract” on the Google site and Google Scholar. The primary data sources used consisted of national journals, international journals, and the WHO website. Articles were screened using the inclusion criteria of Indonesian and English journals published in the last ten years. Of the toxicity study articles discussing 10 herbs-induced liver injury (HILI) and 10 drug-induced liver injury (DILI) that we reviewed, it is known that the dose consumed has a more significant effect on the incidence of hepatotoxicity and nephrotoxicity than the duration of administration with low doses. However, the period of administration with high doses has a significant relationship with liver and kidney damage. Therefore, disseminating safety studies to the public is very important to maximize drug efficacy and avoid hepatotoxicity and nephrotoxicity.

Keywords: *herbal medicine (HM); hepatotoxicity; nephrotoxicity; Asia; safety*

Introduction

Herbal medicine (HM) is part of alternative health care in the future.[1] According to the World Health Organization (WHO), 60% of the world's population depends on HM. Almost 70-80% of the people from developing countries rely on HM as an immediate need for health care.[2] One of the continents with the most significant number of developing countries in Asia.[3] Asian medicinal plants account for 50% of the export

P-ISSN: 2087-0337
E-ISSN: 2715-9949

quantity and 45% of global revenue from traditional medicines. Two countries that play a significant role in this are China and India.[4] Data from the Southeast Asian Institute of Thai-Chinese Medicine in 2010 showed that less than 1% of the population used acupuncture and 1–19% used Chinese HM. The absence of confidence in the side risks associated with synthetic drugs makes the use of HM much in demand [5], mainly because of their secondary metabolite content.[6]

Secondary metabolites in plants have been shown to possess pharmacological activity to treat chronic and acute diseases, especially preventive therapy.[7] With increasing healthy lifestyles using natural ingredients, drug safety should focus on attention apart from its efficacy effects.[8] Safety is closely related to the quality control of HM.[9] However, the limitations of scientific studies on evidence of efficacy and safety make HM still sceptical in the medical community. The lack of information regarding the safety of using HM in the general public is feared to be consumed more than the prescribed safe dose. This will be very dangerous considering the presence of nephrotoxic phytochemical compounds such as aristolochic acid and alkaloids.[10,11] Paracelsus (Father of Toxicology) said in German, "*Alle Dinge sind Gift und nichts ist ohne Gift, allein die Dosage machine, dass ein Ding kein Gift ist*," which means "Everything is poison and nothing is without poison. Only the dose determines that something is non-toxic".[12] Therefore, this review article systematically discusses the use of plant extracts in therapy and their dosage, the mechanism of nephrotoxicity, and hepatotoxicity by plant extracts, to increase awareness of the importance of dosage.[13]

Methods

The search was conducted using the keywords "Herbal Medicine," "Safety," "Nephrotoxicity," "Hepatotoxicity," "Asia," "extract" through the Google site and GoogleScholar. The primary data sources used consisted of national journals, international journals, and the WHO website. Articles were filtered with the inclusion criteria of accredited Indonesian and English journals focusing on hepatotoxic and nephrotoxic activity published in the last ten years.

Results

Table 1. Effect of Hepatotoxicity by Herbal Extracts

No.	Plant Names	Compound	Methods	Hepatotoxic Doses	Sources
1.	"Dewa" (*Gynura divaricata*) Leaf aqueous extract	Pyrrolizidine alkaloid	Acute toxicity test (in Sprague Dawley rats with breast cancer).	LD50 = ≥ 750 mg/kg BW p.o. has been observed increases SGOT and SGPT	[14]
2.	"Gaharu" (*Aquilaria malaccensis*) Leaf aqueous extract	terpenoids, xanthonoids, flavonoids, benzophenones, phytosterols, phenolic	Acute and sub-acute toxicity test (in Sprague-Dawley (SD) rats).	• LD50 (acute toxicity) = >2000 mg/kg p.o. has been observed increases	[15]

P-ISSN: 2087-0337
E-ISSN: 2715-9949

		acids,fatty acid, 4'-hydroxyacetanilide		ALP and ALT. • LD50 (sub-acute toxicity) = >2000 mg/kg p.o. has been observed lymphocytic infiltration and vascular congestion.	
3.	Pulai bark methanol extract (*Alstonia scholaris*)	Flavonoids, tannins, saponins, alkaloids, steroids, and triterpenoids	Acute and subacute toxicity tests (in Sprague-Dawley (SD) rats).	• LD50 (acute toxicity) = > 2000 mg/kg p.o. • LD50 (subacute toxicity) = ≥ 500 mg/kg p.o. has been observed degeneration (lesions) and centrilobular necrosis in the liver.	[16,17]
4.	*Epigynous auritum* ethanol extract (EAE)	Glycosides	Acute and subacute toxicity test (in mice)	• LD50 (acute toxicity) = > 5000 mg/kg p.o. • LD50 (subacute toxicity) = ≥ 1250 mg/kg has been observed liver toxicity.	[18]
5.	"Parang Romang" (*Boehmeria virgata* (Forst) leaf ethanolic extract	Alkaloids	Acute and subacute toxicity tests (in rats)	LD50 (subacute toxicity) = ≥ 250 mg/kg p.o. has been observed hydrophilic degeneration of liver cells.	[19]

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6.	Sipatah-patah (*Cissus quadrangula* S.) stem ethanol extract	Alkaloids, tannins, terpenoids, flavonoids.	Subacute toxicity test (in mice)	LD50 = ≥ 105 mg/kg p.o. has been observed degeneration and necrosis of liver cells.	[20]
7.	Bay leaf (*Syzygium polyanthum* W.) ethanolic extract	Flavonoids, alkaloids, saponins, and tannins	Subchronic toxicity test (in Sprague-Dawley rats)	LD50 (in male rats) = ≥ 1000 mg/kg p.o. has been observed histoarchitectural defects in hepatocytes.	[21]
8.	Ketapang (*Terminalia catappa*) leaf aqueous extract	Tannins, triterpenoids, flavonoids, alkaloids, steroids, resins, and saponins.	Subchronic toxicity test (in mice)	LD50 = ≥ 125 mg/kg p.o. has been observed increased cell swelling and necrosis with increasing dose.	[22]
9.	*Pericampylus glaucus* L. leaf ethanol extract	Alkaloids	Acute and subacute toxicity tests (in mice)	• LD50 (acute toxicity) = unobserved. • LD50 (subacute toxicity) = ≥ 600 mg/kg p.o.has been observed increases SGOT and SGPT.	[23]
10.	*Retama raetam (RR)* fruit methanol extract	Flavones, quinolizidine alkaloids, piperidine alkaloids, lupin alkaloids, polysaccharides, and essential oils	Acute and subacute toxicity tests.	• LD50 (acute toxicity) = 1995 mg/kg p.o. • LD50 (subacute toxicity) = ≥ 500 mg/kg p.o. has been observed degeneration hepatocyte.	[24]

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E-ISSN: 2715-9949

Table 2. Effect of Nephrotoxicity by Herbal Extracts

No.	Plant Name	Compound	Methods	Nephrotoxic Doses	Sources
1.	Calpoureh (*Teucrium polium* L.) ethanol extract	Salvigenin, cirsiliol, α- and β-pinen, sabinene, myrcene, germacrene D, limonene, β-caryophyllene, and spathulenol.	Subchronic toxicity test. (in Wistar rats)	LD50 = ≥ 50 mg/kg i.p. has been observed that 28 days after the injection was stopped, there was kidney damage	[25]
2.	Mahogany Seed (*Swietenia mahagoni* Jacq.) ethanol extract	Triterpenoids	Subchronic toxicity test. (in Wistar rats)	LD50 ≥ 50,96 mg/200g p.o. has been observed increases creatinine and urea	[26]
3.	*Stachys lavandulifolia* ethanol extract	Phenylpropanoids, Germacrene-D, β-phellandrene, β-pinene, myrcene dan α-pinene	Subchronic toxicity test. (In Wistar rats)	LD50 = ≥ 140 mg/kg i.p. has been observed that one month after the injection was stopped, there was kidney damage	[27]
4.	Leaf of Karamunting (*Rhodomyrtus tomentosa,* H.) ethanol extract.	Saponin	Acute toxicity test: pretest and posttest control group design. (in rats)	LD50 = ≥ 600 mg/kg BW has been observed to increase creatinine and urea	[28]
5.	*Aristolochia longa* L. aqueous extract.	Aristolochic Acid	Acute and subchronic toxicity tests. (in Swiss albino rats)	LD50 (subchronic toxicity) = ≥ 2,5 g/kg p.o. has been observed for three weeks showed mild tubular atrophy; for six weeks, tubular necrosis occurred.	[29]

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6.	Cinnamon (*Cinnamomum cassia)* extract	Coumarin	Acute, subchronic, and genotoxicity test. (in F344 mice)	LD50 = ≥ 2000 mg/kg p.o. It has been observed to induce an increase in kidney weight.	[30]
7.	Ma huang/Ephedra Herba (*Ephedra sinica* Stapf.) aqueous extract	Ephedrine and pseudoephedrine	Subchronic toxicity test. (in F344 mice).	LD 50 = ≥ 1000 mg/kg p.o. has been observed to increase the incidence and severity of tubular basophilia.	[31]
8.	*Houttuynia cordata* ethanol extract	β-myrcene and 2- undecanone	Acute and sub-acute toxicity tests. (in Sprague Dawley rats)	• LD50 (acute toxicity) = > 2000 mg/kg p.o. • LD50 (Subacute toxicity) = ≥ 500 mg/kg p.o. has been observed to exhibit renal toxicity.	[32,33]
9	Garlic (*Allium sativum*) ethanol extract	Glycosides	Subchronic toxicity test. (in Wistar rats)	LD50 = ≥ 400 mg/kg p.o. has been observed degeneration of tubular epithelial cells lining Bowman's capsule, tubular dilatation, and enlargement of Bowman's space.	[34]
10.	*Balm (Melissa officinalis L.) hydro-alcoholic extract*	Eugenol glucoside,rosmarinic acid, cynaroside,cosmosin,rhamnocitrin,isoquercitrin, carnosic acid, ursolic, and oleanolic	Subchronic toxicity test.	LD50 = ≥ 1200 mg/kg p.o. Prominent lesions, tubular necrosis, glomerular atrophy, and congestion have been observed.	[35]

P-ISSN: 2087-0337
E-ISSN: 2715-9949

Discussion

Prevalence of Herbal Medicines Use in Asia

The use of HM in Asia and Indonesia is estimated to increase over the years. In some Asian and African countries, about 80% of the rural population depends on traditional medicine for primary health care.[36] China and India are the Asian countries that play the most role in the development of HM. India has played an essential part for thousands of years in managing medicinal plants as alternative therapies.[37] In 2016, a study in 32 primarily high-income countries stated that the prevalence rate of traditional therapy use over the past 12 months averaged 26.4%, ranging from less than 10% in some Eastern European countries to more than 50% in China, South Korea, and the Philippines.[38] In ASEAN, the highest use of herbal therapy was in Malaysia (55.6%), Singapore (among older adults) (42.7%), the Philippines (6.3%), Cambodia (5.4%), Vietnam (3.5%), Thailand (2.6%) and Indonesia (2.0%).[39] In Indonesia, based on an extensive national household survey in 2013, 30.4% of families used traditional medicine for health care.[40] The current use of conventional medicine is generally only found in patients with cancer or malignant tumors (14.4%), followed by arthritis/rheumatism (11.3%), high cholesterol (11.3%), stroke (10.2%), diabetes (9.9%), kidney disease (9.7%), liver disease (8.0%), hypertension (7.2%), and memory-related diseases (6.8%).[41]

Mechanism of Hepatotoxicity

The liver is part of the human organ that is very sensitive to injury due to its vital role in neutralizing toxins.[42] Therefore, excessive exposure to toxins from food, beverages, drugs (synthetic and non-synthetic (HM)) has the potential to cause liver injury (hepatotoxicity).[43] Hepatotoxicity induced by irregular drug use is commonly known as DILI (Drug-Induced Liver Injury).[44] Hepatotoxicity due to HM is commonly known as HILI (Herb-Induced Liver Injury).[45]

HILI is liver damage which is one of the causes is triggered by the use of plants with unknown toxicity limits.[46] The mechanism of HILI is divided into three stages, starting from early liver cell damage through direct cell stress, mitochondrial suppression, and/or specific immune response. Following the mitochondrial permeability transition (MPT) stage, early injury can induce MPT, and cellular stress directly induces MPT via internal pathways. The last stage is hepatocyte death; MPT can cause necrosis or apoptosis depending on ATP defense availability, and regeneration abilities can restore the damaged liver cells. Any action taken involves various environmental and genetic factors, and the degree of liver damage varies.[47]

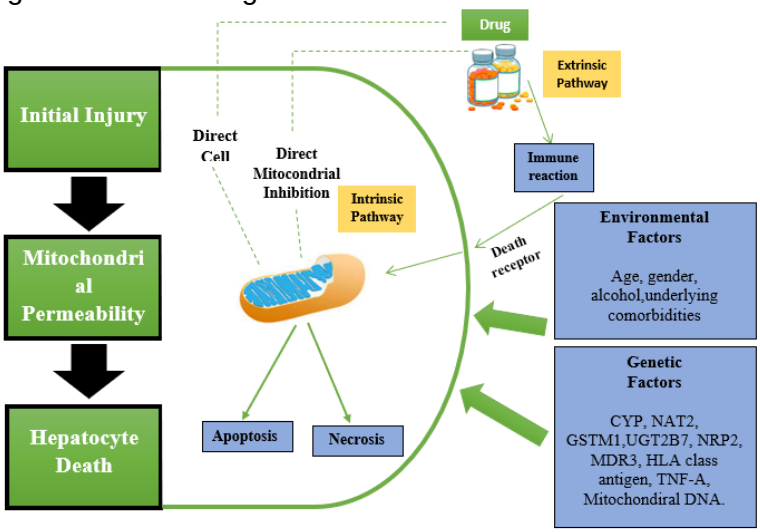

Figure 1. Mechanism of Drug-Induced Liver Injury [48]

P-ISSN: 2087-0337
E-ISSN: 2715-9949

The level of hepatotoxicity caused by HILI is classified into three types, including hepatocellular, cholestatic, and mixed.[45] These were classified according to the value of the R ratio obtained by comparing the results of the initial measurement of alanine aminotransferase (ALT) with alkaline phosphatase (ALP) using multiples of the upper limit of the normal range for both values. $R \geq 5$ indicates hepatocellular liver injury; $R \leq 2$ is cholestatic; and $2 < R < 5$ is mixed.[49,50] There are two critical factors for HILI development, including the level of drug exposure (dose) and the adaptive immune response. Drug exposure and the nature of the drug administered play a significant role in the early stages of cell damage. Once damaged, both innate and adaptive responses emerge and play an essential role in triggering inflammation and tissue injury.[47]

Mechanism of Nephrotoxicity

Kidneys are part of the functional unit of the body, containing about 1 million nephrons, one of which functions play an essential role in neutralizing drug toxicity. The loss of one or more cells in the nephron can cause functional kidney damage.[51] The term nephron damage due to exogenous drugs/toxins is known as nephrotoxicity.[52]

Nephrotoxicity has a relationship with the use of HM. The use of HM that has been shown to cause nephrotoxicity directs their toxic effects through one or more pathogenic mechanisms.[53] There are different mechanisms of nephrotoxicity, including renal tubular toxicity, inflammation, glomerular damage, crystal nephropathy, and thrombotic microangiopathy. Toxic substances and drugs induce oxidative stress that causes damage to the renal tubules, thereby causing potential damage to the renal tubular transport system.[54] This oxidative stress arises due to the presence of lipopolysaccharide (LPS), which activates NF-B and mitogen-activated protein kinases (MAPKs).[55]

One well-known example of nephrotoxicity due to HM is triggered by aristolochic acid.[56] Aristolochic acid (AA) is a group of nitrophenanthrene carboxylic acid compounds found in the Aristolochiaceae plant family, consisting of aristolochic acid I (AAI) and aristolochic acid II (AAII), which are distinguished by the presence of an O-methoxy group at position 8 for AAI while AAII does not have an O-methoxy group at position 8 (indicated by a bold arrow in Figure 2).[57]

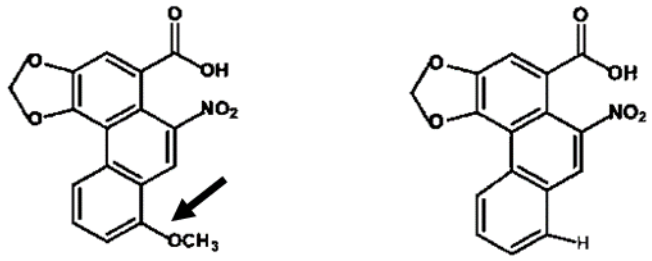

Figure 2. Chemical Structure of AAI (left) and AAII (right) [58]

Based on research, AA has been associated with the induction of oxidative stress (ROS) and apoptosis.[59] Exposure to AAI in the proximal renal tubule that enters through OAT1/OAT3(organic anion transporter 1/organic anion transporter 3) induces ROS that can cause DNA damage (TP53, OGG1), induce ER(endoplasmic reticulum) and mitochondrial stress, or activate the MAPK(mitogen-activated protein kinase) pathway.[60] ER induction causes an increase in Ca^{2+}, which causes the mitochondria to release cytochrome C (Cyt C). Cyt C activates caspase-3, resulting in apoptosis. Endoplasmic reticulum (ER) and AAI-induced mitochondrial stress were also associated with increased protein complexes (eIF2a, CHOP, GRP78) that could induce cell apoptosis.

As for the interaction of AAI with MAPK, the induction of apoptosis is related to the activation of p38 or p53 (as demonstrated in Figure 3).[57]

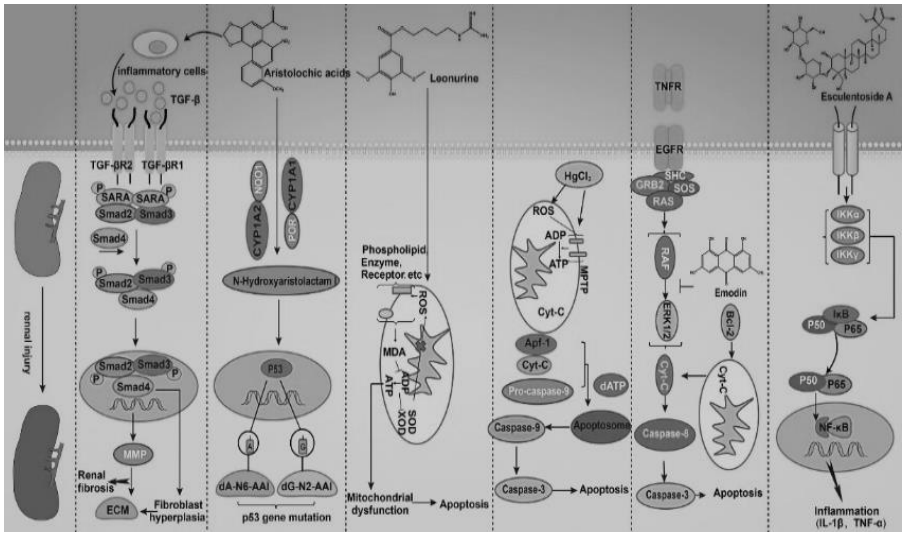

Figure 3. Mechanism of Herb Induced Kidney Injury [61]
ROS(reactive oxygen species); CYP1A1(cytochrome P450 family 1 subfamily A member 1); CYP1A2(cytochrome P450 family 1 subfamily A member 2); MAPK(mitogen-activated protein kinase); Cyt C(cytochrome C); SARA(smad anchor for receptor activation); TGF-βR1/TGF-βR2 (transforming growth factor-beta receptor 1/ transforming growth factor-beta receptor 2); ECM(extracellular matrix); MMP(matrix metalloproteinase); MDA(Malondialdehyde); TNFR(tumor necrosis factor receptors); EGFR(epidermal growth factor receptor); ERK1/2(extracellular signal regulated kinase ½); Bcl-2(B-cell lymphoma 2); ATP (adenosine tri-phosphate); ADP(adenosine diphosphate); SOS(son of sevenless); SHC(src homology and containing protein); GRB2 (growth factor receptor-bound protein 2).

Hepatotoxic and Nephrotoxic-Inducing Herbs

Hepatotoxicity is a severe event of the liver that may cause death if not adequately controlled. SGOT, SGPT, and histopathological tests can identify hepatotoxicity.[62] Hepatotoxicity can occur due to accidental contamination with non-herbal drugs causing hepatotoxicity (e.g., NSAIDs) or the content of secondary metabolites of some HM.[63,64] Sometimes, hepatotoxicity is also associated with self-medication without medical assistance, misdiagnosis, and the presence of comorbid diseases.[65–67] The lack of information regarding HM toxicity studies may also contribute to hepatotoxicity.[68] HM consists of unrefined plant parts or plant extracts containing several elements that are generally considered to work synergistically.[69] The following are examples of several plant toxicity studies on hepatotoxicity shown in Table 1**.**

Likewise, nephrotoxicity, as well as hepatotoxicity, has a relationship with HM. Several herbal plants used in the long term, from the results of toxicity studies, have been observed to induce tubular necrosis and atrophy.[29] Urea and creatinine levels can also observe the glomerular function. However, the histopathological test remains the golden standard in identifying nephrotoxicity.[70] The following are some examples of plant toxicity studies on nephrotoxicity shown in Table. 2.

Of some of the articles that we have reviewed, it is not entirely safe to use herbal remedies. Several herbal plants have hepatotoxicity and nephrotoxicity activity. It is known that increasing the dose consumed more affects the incidence of hepatotoxicity and nephrotoxicity than the duration of administration with low doses. However, prolonged exposure will significantly affect liver and kidney damage if high doses are

used. Therefore, it is crucial to know the toxic dose of HM use and further research to avoid lethal hepatotoxic and nephrotoxic.[71,72]

Conclusion

The use of HM is closely related to the dose. Of the results of toxicity studies of several plants, it was observed that there was cell degeneration activity that worsened the functional conditions of the liver and kidneys with increasing doses. Therefore, disseminating information regarding safety studies to the public is very important to maximize drug efficacy and avoid lethal hepatotoxicity and nephrotoxicity.

Acknowledgments

The authors thank the Rector of Universitas Padjadjaran for funding the publication fee of this article via the Universitas Padjadjaran Academic-Leadership grant of Prof. Dr. Dra. Jutti Levita, M.Si., Apt. batch 2021.

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