

## Hepatoprotective Potential of *Rhizophora mucronata*: A Literature Review of Phytochemical Constituents, Molecular Mechanisms, and Preclinical Evidence

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### Abstract

*Rhizophora mucronata* is a mangrove species that contains various secondary metabolites and has been extensively investigated for its biological activities. This literature review aimed to evaluate the hepatoprotective potential of *Rhizophora mucronata* based on its phytochemical constituents, molecular mechanisms, and available preclinical evidence. The literature was searched through several scientific databases using combinations of keywords related to *Rhizophora mucronata*, hepatoprotection, liver injury, oxidative stress, antioxidants, inflammation, apoptosis, and bioactive compounds. Relevant studies were subsequently synthesized narratively based on their phytochemical characteristics, biological activities, potential mechanisms, and in vivo findings. The synthesis indicated that *Rhizophora mucronata* contains phenolic compounds, flavonoids, tannins, terpenoids, alkaloids, saponins, and various other metabolites that may contribute to its antioxidant and anti-inflammatory activities. Several in vivo studies have shown that *Rhizophora mucronata* extracts can reduce biochemical and histopathological alterations in the liver in models of liver injury induced by toxic substances or metabolic conditions. These effects are thought to be associated with the reduction of oxidative stress, restoration of antioxidant system balance, modulation of inflammation, and inhibition of hepatocyte cell death. Nevertheless, the available evidence is still predominantly based on experimental studies and remains insufficient to establish clinical efficacy. Further research is needed to identify the active compounds, specific molecular targets, optimal doses, long-term safety, and translational potential of *Rhizophora mucronata* as a hepatoprotective candidate.

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## 1. INTRODUCTION

The liver is the primary metabolic organ responsible for nutrient metabolism, xenobiotic biotransformation, homeostatic regulation, and detoxification processes. Exposure to drugs, alcohol, chemicals, metabolic disorders, and inflammatory conditions can lead to the accumulation of reactive oxygen species (ROS), impaired cellular function, and liver tissue damage. Excessive oxidative stress can trigger lipid peroxidation, protein and nucleic acid damage, mitochondrial dysfunction, and the activation of cell death pathways. These processes can also interact with inflammatory responses, thereby exacerbating hepatocyte damage [1].

Environmental resources, particularly *Rhizophora mucronata*, can be explored for their potential development as hepatoprotective agents. Phenolic compounds and flavonoids, for example, are known for their ability to scavenge free radicals and have the potential to modulate various pathways associated with oxidative stress and inflammation. Mangrove plants are an interesting source of natural compounds because they produce a variety of secondary metabolites as part of their adaptation to extreme coastal environments. One mangrove species commonly found in tropical regions is *Rhizophora mucronata*. Various parts of this plant, including the leaves, stem bark, roots, fruits, and propagules, have been reported to contain groups of secondary metabolites such as flavonoids, phenolics, tannins, alkaloids, saponins, steroids, and terpenoids [2]. UHPLC-QTOF-MS analysis of various plant parts identified a large number of phenolic metabolites, including phenolic acids, flavonols, flavones, anthocyanins, tyrosols, lignans, alkylphenols, and stilbenes [3]. This diversity provides a biological basis for the development of *Rhizophora mucronata* as a source of candidate bioactive compounds.

The antioxidant activity of *Rhizophora mucronata* has been reported in various parts of the plant. Leaf extracts, for example, have been shown to contain flavonoids, phenolic compounds, tannins, saponins, and terpenoids, as well as free radical-scavenging activity [2]. Another study on the leaves of *Rhizophora mucronata* from Indonesia also showed differing antioxidant activities depending on the solvent used, indicating that solvent polarity can influence the composition of the extracted bioactive compounds. Furthermore, research on *Rhizophora mucronata* propagules successfully identified compounds such as caffeoylquinic acid derivatives, epicatechin, and procyanidin B2 [4].

The relationship between antioxidant activity and liver protection becomes important because oxidative stress is one of the mechanisms involved in various forms of hepatocellular injury. More direct evidence of the hepatoprotective activity of *Rhizophora mucronata* has been reported in animal models. Research shows that the aqueous leaf extract of *Rhizophora mucronata* exhibits hepatoprotective effects in streptozotocin-induced diabetic rats [5]. Another study shows that the stem bark extract of *Rhizophora mucronata* can reduce liver damage caused by ethanol exposure in mice, accompanied by decreased markers of oxidative stress and apoptosis [6].

This evidence is further reinforced by experimental research evaluating the safety of *Rhizophora mucronata* stem bark extract. Repeated administration for 28 days in mice showed no significant histopathological changes in the liver at the tested doses. Recent studies also continue to expand the evidence regarding the biological activities of *Rhizophora mucronata*, including the antioxidant and anti-inflammatory activities of its leaf extract [6]. Nevertheless, literature regarding *Rhizophora mucronata* remains scattered across phytochemical studies, antioxidants, general pharmacology, and several hepatotoxicity models. The relationship between phytochemical content → antioxidant/anti-inflammatory activities → specific mechanisms → liver tissue protection has not been extensively summarized in a specific manner. Therefore, this literature review was conducted to evaluate the hepatoprotective potential of *Rhizophora mucronata* by focusing the discussion on three main aspects: phytochemical composition, molecular mechanisms potentially underlying the hepatoprotective effects, and available preclinical evidence.

## 2. RESEARCH METHODS

This study is a narrative literature review that aims to identify and synthesize information regarding the hepatoprotective potential of *Rhizophora mucronata*,

particularly concerning its phytochemical content, biological activities, molecular mechanisms, and preclinical evidence. The literature search was conducted through PubMed, Google Scholar, and other relevant scientific databases using a combination of keywords: *Rhizophora mucronata*, hepatoprotective, liver injury, liver damage, hepatotoxicity, oxidative stress, antioxidant, inflammation, apoptosis, phytochemical, and bioactive compounds.

### 3. RESULTS AND DISCUSSION

#### 3.1. Phytochemical Composition of *Rhizophora mucronata*

The synthesis results indicate that *Rhizophora mucronata* possesses a diverse composition of secondary metabolites. The most consistently reported compound groups include phenolics, flavonoids, tannins, alkaloids, saponins, terpenoids, steroids, and glycosides [7]. Differences in composition can be found among plant parts and types of solvents used in the extraction process. Metabolomic analysis provides a more detailed overview regarding the complexity of phenolic compounds in *Rhizophora mucronata*. From various extracts of leaves, roots, twigs, and fruits, various groups of phenolic compounds were putatively identified, including 104 phenolic acids, 103 flavonols, 94 flavones, 71 anthocyanins, 66 tyrosols, 29 lignans, 15 alkylphenols, and 10 stilbenes [8]. These findings indicate that the biological activity of *Rhizophora mucronata* likely does not stem from a single compound, but is rather the result of interactions among various bioactive components.

Through a study by Yunos et al., several phenolic compounds were identified in *Rhizophora mucronata* propagules, including 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, epicatechin, and procyanidin B2 [9]. These compounds chemically possess characteristics that support antioxidant activity, although the direct relationship of each compound to hepatoprotection still requires specific experimental confirmation. Recent research also demonstrates the presence of flavonoids, tannins, and alkaloids, along with antioxidant and anti-inflammatory activities [10]. Thus, the phytochemical profile of *Rhizophora mucronata* provides a sufficiently strong foundation to explain why this plant holds potential as a candidate source of hepatoprotective agents, even though the causal relationship between specific compounds and hepatoprotective effects has not been fully established.

#### 3.2. Antioxidant Activity

Oxidative stress is one of the key mechanisms in the development of hepatocellular injury. Elevated levels of ROS can lead to membrane damage through lipid peroxidation, alterations in protein structure, DNA impairment, and mitochondrial dysfunction [11]. Therefore, the ability of a natural product to scavenge free radicals and maintain the balance of the antioxidant system serves as an essential foundation for evaluating its hepatoprotective potential. Numerous studies have demonstrated the antioxidant activity of *Rhizophora mucronata*. A study on leaf extracts using LC-MS identified a range of flavonoids, phenolic acids, lignans, alkaloids, and terpenoids, while simultaneously demonstrating the antioxidant activity of the extract [12]. Metabolomic studies across various plant parts also revealed the presence of phenolics, flavonoids, flavanols, tannins, and triterpenoids, which correlate with the biological activity of the extracts [13].

Research on *Rhizophora mucronata* leaves from the Surabaya mangrove region showed the presence of flavonoids, saponins, steroids, triterpenoids, and tannins in extracts using various solvents. Differences in antioxidant activity among the extracts

indicate that the type of solvent can influence the quantity and profile of the extracted metabolites [14]. These findings are relevant to hepatoprotective potential because phenolic and flavonoid compounds can act as free radical scavengers. However, antioxidant activity measured via chemical assays such as DPPH cannot be directly equated to a hepatoprotective effect. Such *in vitro* activity is more appropriately viewed as supporting evidence that needs to be confirmed through cellular and animal models.

### 3.3. Hepatoprotective Mechanism

The hepatoprotective potential of *Rhizophora mucronata* can be understood through the interrelationship between its secondary metabolite content and its antioxidant, anti-inflammatory, and liver cell protection activities. Various studies have shown that *Rhizophora mucronata* contains phenolic compounds, flavonoids, tannins, terpenoids, alkaloids, saponins, as well as other bioactive metabolites [13]. The diversity of these compounds is thought to contribute to the plant's biological activity through interconnected mechanisms, particularly in controlling oxidative stress and inflammatory responses.

Oxidative stress represents a key mechanism in the occurrence of hepatocyte damage. Elevated levels of reactive oxygen species (ROS) can induce membrane lipid peroxidation, protein and DNA damage, mitochondrial dysfunction, and activate cell death pathways. The phenolic and flavonoid content of *Rhizophora mucronata* possesses antioxidant capabilities that help scavenge free radicals and mitigate oxidative damage [15]. This activity has been demonstrated through various antioxidant assays on leaf extracts and other plant parts. Differences in activity across extracts also indicate that solvent types and plant parts can influence the resulting compound composition [16].

These antioxidant activities are potentially linked to hepatocyte protection. In studies utilizing a carbon tetrachloride-induced hepatotoxicity model, *Rhizophora mucronata* extracts were reported to improve several biochemical parameters associated with liver damage, including transaminase levels, alkaline phosphatase, bilirubin, and lactate dehydrogenase [17]. These findings provide preliminary evidence that the biological activity of *Rhizophora mucronata* is not strictly limited to *in vitro* antioxidant testing, but can also exert protective effects in animal models.

Such potential mechanisms are also evident in ethanol-induced liver injury models. Administration of *Rhizophora mucronata* stem bark extract was reported to lower oxidative stress indicators and attenuate liver tissue alterations resulting from ethanol exposure [18]. This effect was accompanied by a decrease in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) expression, indicating the potential involvement of inflammatory response modulation in liver protection. Furthermore, the extract was reported to reduce DNA fragmentation and the number of apoptotic cells, suggesting that the protection provided likely encompasses the inhibition of hepatocyte damage and cell death.

The relationship between antioxidant and anti-inflammatory activities becomes vital because oxidative stress and inflammation can form a cycle that exacerbates liver injury. Excessive ROS can activate inflammatory pathways, whereas inflammatory mediators can increase ROS production and perpetuate cell damage. Consequently, the ability of *Rhizophora mucronata*'s bioactive compounds to control both processes holds the potential to yield broader hepatoprotective effects compared to radical-scavenging activity alone. Research on *Rhizophora mucronata* leaf extracts has similarly demonstrated anti-inflammatory and antioxidant activities, supporting the likelihood of a multi-target mechanism. Hepatoprotective evidence has also been reported in

metabolic disorder models. In streptozotocin-induced diabetic rats, aqueous leaf extracts of *Rhizophora mucronata* exhibited effects related to liver protection [5]. Diabetic conditions are known to be associated with elevated oxidative stress and metabolic alterations that impact liver tissue. Therefore, the antioxidant activity and metabolic modulation possessed by *Rhizophora mucronata* potentially contribute to the effects observed in this model.

The diversity of metabolites present in *Rhizophora mucronata* also points to the possibility of a multi-component hepatoprotective mechanism. Metabolomic analyses have identified various groups of phenolic compounds, including phenolic acids, flavonols, flavones, anthocyanins, lignans, and stilbenes [16]. Several of these compounds are known to possess biological activities related to the management of oxidative stress and inflammation. However, the presence of a compound in an extract does not directly prove that it is the sole component responsible for the hepatoprotective effect. Causal relationships between specific compounds and molecular targets still require validation through experimental research.

### 3.4. Preclinical Evidence of Hepatoprotective

An initial study by Ravikumar and Gnanadesigan evaluated several parts of *Rhizophora mucronata* in a carbon tetrachloride (CCl<sub>4</sub>)-induced hepatotoxicity model. The stilt root extract demonstrated superior hepatoprotective activity compared to other plant parts. Administration of the extract at 75–300 mg/kg was reported to lower biochemical parameters such as SGOT, SGPT, ALP, bilirubin, cholesterol, glucose, and LDH compared to the hepatotoxin group [17]. This finding serves as direct evidence that *Rhizophora mucronata* can modulate liver injury parameters in experimental models.

Streptozotocin-induced diabetes model, the aqueous leaf extract of *Rhizophora mucronata* was also reported to exhibit hepatoprotective effects [5]. Model tersebut penting karena diabetes dan hiperglikemia dapat meningkatkan stres oksidatif dan memperburuk gangguan fungsi hati. This model is particularly relevant as diabetes and hyperglycemia can exacerbate oxidative stress and aggravate liver dysfunction. More recent evidence was provided by Chitra et al. using an ethanol-induced liver injury model. *Rhizophora mucronata* stem bark extract was administered at several doses prior to ethanol exposure. The results demonstrated a reduction in histopathological damage, decreased TNF- $\alpha$  expression, reduced DNA fragmentation, and favorable alterations in oxidative stress parameters [8]. Consequently, this study establishes evidence linking antioxidant, anti-inflammatory, and anti-apoptotic activities to liver protection effects. Alongside efficacy, safety aspects are equally essential in natural product development. Acute and subacute toxicity studies of *Rhizophora mucronata* stem bark extract showed that repeated administration for 28 days at tested doses produced no histopathological abnormalities in the liver, kidneys, lungs, or spleen [18]. These results provide preliminary evidence regarding the extract's tolerability, though they remain insufficient to establish long-term safety in humans.

Research on coffee-like product extracts derived from *Rhizophora mucronata* fruits in a mouse model with lipopolysaccharide-induced systemic inflammation also reported improvements in several liver injury parameters and histopathological changes at higher doses [19]. Temuan ini memperluas bukti preklinik mengenai potensi hepatoprotektif *Rhizophora mucronata*, walaupun jenis bahan, metode ekstraksi, model penyakit, dan komposisi fitokimia berbeda dari penelitian sebelumnya. This finding broadens the preclinical evidence regarding the hepatoprotective potential of

*Rhizophora mucronata*, even though the source material, extraction methods, disease models, and phytochemical compositions differ from prior studies.

#### 4. CONCLUSION

*Rhizophora mucronata* holds potential as a natural source with hepatoprotective activity, based on a combination of phytochemical, antioxidant, anti-inflammatory, and preclinical evidence. Various parts of the plant contain secondary metabolites such as phenolic compounds, flavonoids, tannins, alkaloids, saponins, and terpenoids, which potentially contribute to its biological activities. In vivo evidence demonstrates that *Rhizophora mucronata* extracts can attenuate several indicators of liver injury, oxidative stress, inflammation, apoptosis, and histopathological alterations across various experimental models.

The mechanisms most consistently supported by the literature include the management of oxidative stress, modulation of the inflammatory response, and reduction of hepatocyte death. However, heterogeneity in plant parts, extraction methods, dosages, and research models means that the available evidence is currently insufficient to determine the specific active compounds and optimal regimens. Consequently, *Rhizophora mucronata* can be viewed as a promising candidate hepatoprotective agent at the preclinical stage, but further mechanistic, toxicological, pharmacokinetic, extract standardization, and clinical studies are required to establish its therapeutic relevance in humans.

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