UNIVERSITY OF LIFE SCIENCES ”KING MIHAI I” FROM TIMISOARA
”YOUNG PEOPLE AND MULTIDISCIPLINARY RESEARCH IN APPLIED LIFE SCIENCES”

05-06 November 2026



Curcuma longa L. and *Silybum marianum* (L.) Gaertn. in Acetaminophen-Induced Hepatotoxicity: Mechanistic Basis and Potential for Combined Hepatoprotection

Maria-Larisa Rusu[1], Harieta Muntean[1], Mihai Folescu[1], Anca Ciura[1], Daiana Cocoș[1], Romeo Teodor Cristina[1], Eugenia Dumitrescu[1]

[1]*University of Life Sciences “KingMihai I” in Timișoara*

Abstract: *Acetaminophen-induced hepatotoxicity represents one of the best-characterized models of acute liver injury and is widely used to investigate pathophysiological mechanisms and to evaluate potential hepatoprotective agents. The bioactivation of acetaminophen through the cytochrome P450 system leads to the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), whose accumulation results in depletion of hepatic glutathione stores, oxidative stress, mitochondrial dysfunction, activation of the inflammatory response, and hepatocellular necrosis, predominantly in the centrilobular region. In this context, natural compounds with antioxidant and anti-inflammatory properties represent an important area of research. Curcuma longa L. and Silybum marianum (L.) Gaertn. are distinguished by multiple hepatoprotective mechanisms, mainly associated with curcumin and silymarin, respectively. Curcumin has been associated with reductions in serum ALT and AST activities, decreased lipid peroxidation, increased glutathione levels and antioxidant enzyme activities, as well as improvement of acetaminophen-induced histopathological alterations. Silymarin exerts antioxidant, anti-inflammatory, hepatocyte membrane-stabilizing, and antifibrotic effects, thereby contributing to the structural and functional protection of the liver. The present review analyzes the mechanisms involved in acetaminophen-induced hepatotoxicity and summarizes the evidence regarding the hepatoprotective effects of Curcuma longa and Silybum marianum, with particular emphasis on their complementary mechanisms and the potential of combined use. Although the association of the two extracts is supported by a plausible mechanistic rationale, evidence demonstrating a synergistic effect superior to monotherapy remains limited, and further studies are required to confirm this hypothesis.*

Keywords: *Curcuma longa; Silybum marianum; curcumin; silymarin; hepatotoxicity; acetaminophen; oxidative stress; hepatoprotection.*

• Introduction

The liver is an essential organ for maintaining homeostasis, playing a central role i n carbohydrate, lipid, and protein metabolism, xenobiotic detoxification, and the r egulation of immune responses. Exposure to hepatotoxic agents can induce oxidat ive stress, mitochondrial dysfunction, inflammation, and cell death. Acetaminophe n-
induced hepatotoxicity represents an experimental model used to investigate thes e mechanisms and is characterized by the formation of the reactive metabolite N-acetyl-p-
benzoquinone imine (NAPQI), glutathione depletion, and the development of cent rilobular necrosis. In this context, extracts from *Curcuma longa* and *Silybum maria num* have attracted considerable interest due *to the*ir antioxidant, anti-inflammatory, and hepatoprotective properties.



Figure 1. *Curcuma longa* and *Silybum marianum*

• Pathophysiological mechanisms of acetaminophen-induced hepatotoxicity

Under overdose conditions, acetaminophen metabolism through the cytochrome P450 system, particularly via the CYP2E1 isoenzyme, leads to excessive formation of the reactive metabolite N-acetyl-p-
benzoquinone imine (NAPQI). Depletion of hepatic reduced glutathione (GSH) sto res promotes the covalent binding of NAPQI to hepatocellular proteins, particularl y mitochondrial proteins, triggering oxidative stress and cellular energy dysfuncti on.
These alterations result in increased production of reactive oxygen species (ROS), lipid peroxidation, reduced ATP synthesis, and activation of the ASK1–
JNK signaling pathway, contributing to the progression of hepatocellular necrosis. The lesions are predominantly localized in the centrilobular region and are accom panied by alterations in hepatic biomarkers and activation of the inflammatory re sponse.

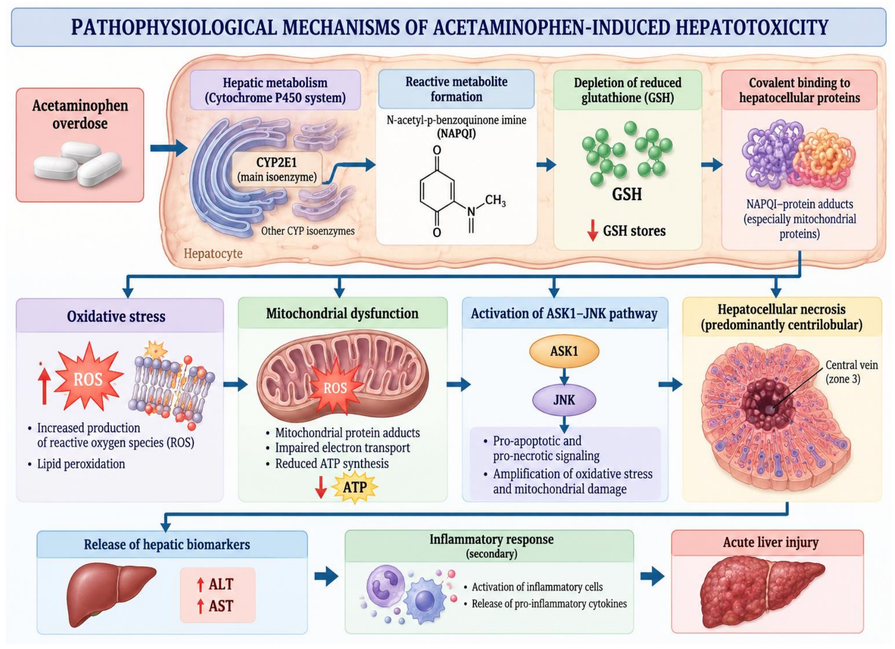


Figure 2. Pathophysiological mechanisms of acetaminophen-induced hepatotoxicity: from NAPQI formation and glutathione depletion to mitochondrial dysfunction, oxidative stress, and centrilobular hepatocellular necrosis.

• Hepatoprotective potential of plant extracts

Curcuma longa contains curcumin, a polyphenol with antioxidant and anti-inflammatory properties. Curcumin activates the Nrf2 signaling pathway, promoti ng the expression of antioxidant enzymes, including HO-
1, SOD, and GST. Furthermore, it inhibits NF-
κB activation, reducing the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-
6. Experimental studies described in the review have demonstrated reductions in ALT, AST, and MDA levels, increased GSH levels, and attenuation of centrilobular n ecrosis.*Silybum marianum* contains silymarin, a complex of flavonolignans whose main active constituent is silibinin. Silymarin inhibits lipid peroxidation, promote s the maintenance of intracellular GSH levels, and stabilizes hepatocyte membran es. Additionally, it exerts anti-inflammatory effects through NF-
κB modulation and antifibrotic effects by inhibiting hepatic stellate cell activation and TGF-
β signaling. In experimental models, silymarin administration has been associated with reduced serum transaminase levels and improvements in histopathological alterations.The combination of curcumin and silymarin exhibits complementary h epatoprotective potential; however, evidence supporting a synergistic effect super ior to individual administration remains limited.

• Conclusions

Acetaminopheninduced hepatotoxicity involves interconnected mechanisms of ox idative stress, mitochondrial dysfunction, and hepatocellular necrosis, associated with characteristic biochemical and histopathological alterations. Extracts from *C. longa* and *S.marianum* exhibit hepatoprotective potential through the modulatio n of endogenous antioxidant systems, attenuation of inflammation, and preservati on of hepatocellular integrity. The experimental rat model (Rattus norvegicus) pr ovides a relevant basis for investigating these effects, although further studies are required to confirm the potential synergistic effects of the two extracts.