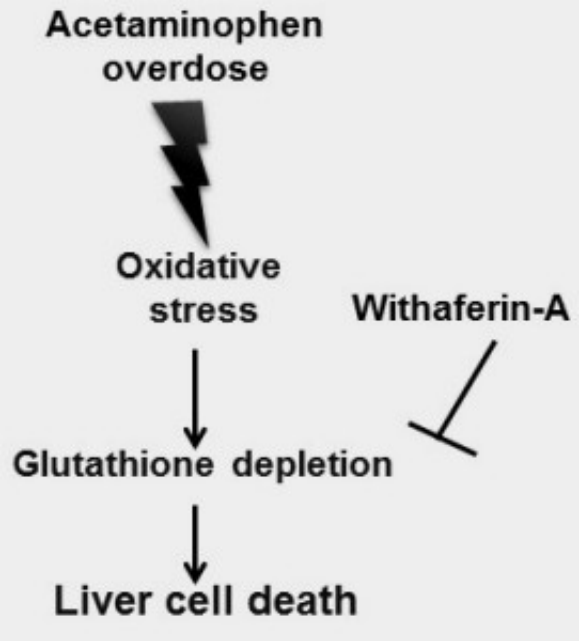
# Withaferin-A, a phytochemical, has potential to reduce liver injury due to acetaminophen overdose

Acetaminophen (APAP), also known as paracetamol, is the most popular over-the-counter drug used for common illnesses such as head and body ache, cold and fever. When administered in therapeutic doses (? 4 grams/24 h for an adult), it is safe. However, every year, its overdose leads to liver injury resulting in thousands of emergency department visits and hospitalizations. In the United States, APAP toxicity is the most common cause of acute liver failure and is the second most common reason for liver failure related transplantation. N-acetyl cysteine (NAC), which provides necessary cysteine for glutathione synthesis is the only available antidote, and is most effective when administered within 8-10 h after APAP overdose. To reduce the burden of APAP-induced liver injury, extensive investigation is underway into the mechanisms of APAP-induced liver cell death to identify key therapeutic targets and develop new antidotes and treatment strategies.




Withania somnifera a plant of Family Solanaceae, commonly known as ashwagandha or winter cherry, has long brown tuberous roots which are thought to have medicinal properties. For years, their extract has been used in Ayurvedic formulations to increase longevity and vitality. Recently, Withaferin-A (WA), one of the active ingredient of Withania somnifera, has been shown to have anti-cancer effects. However, its potential in treatment of clinically relevant liver injury has never been assessed before. Hence, we carried out a study to investigate the therapeutic potential of WA in reducing APAP-induced liver injury. Upon APAP overdose, mice develop liver injury that mimics those in humans. Therefore, APAP-overdosed mice are excellent models to assess the therapeutic

potential of investigational compounds. We treated laboratory mice with 200 mg/kg APAP (equivalent to 14 grams of acetaminophen for 70 kg man). One h later mice were treated with 40 mg/kg WA or its vehicle (control) and euthanized at 4 and 16 h to collect blood and liver. Mice who received WA had far less liver injury compared to mice that did not receive WA. In WA-treated mice, microscopic examination of livers, and blood analysis showed reduced features and circulating markers of liver injury respectively. Upon APAP overdose, glutathione, a major endogenous anti-oxidant in the liver is depleted, which is thought be a major event that results in liver injury; we observed in APAP-overdosed mice that WA prevented glutathione depletion (see Figure). Even in liver cells culture (mouse hepatocytes), WA prevented hydrogen peroxide (oxidative stress generator)-induced cell death by improving GSH levels. Collectively these results demonstrated that WA has excellent anti-oxidant potential and can reduce APAP-induced liver injury. In future, combination therapies employing currently available APAP antidote NAC, plus WA like compounds may be used to reduce the burden of APAP-induced liver injury and need for liver transplantation.

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## Publication

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