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**Butin prevents liver damage triggered by D-galactosamine via regulating lipid peroxidation and proinflammatory cytokines in rodents**

**ABSTRACT**

**Objectives:** Liver damage is becoming a more severe problem around the world. Unfortunately, there is still a great need for clinically effective pharmacological therapy for liver injury. The investigation aimed to assess the favorable outcome of butin hepatoprotective efficacy against D-galactosamine (D-GalN)-produced liver damage in experimental rats.

**Methods:** A single dose of D-GalN 400 mg/kg b. wt. was injected intraperitoneally, 24 hr prior to scarification of rats to cause liver damage. The liver injury was assessed biochemically, investigating parameters like, aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT),  $\gamma$ -glutamyl transferase (GGT), total-bilirubin, -albumin and -protein. Butin (25 and 50 mg/kg b. wt.) was managed for 21<sup>st</sup> days and at the conclusion of experimental period, normal control, D-GalN control and butin treatment group rats for further biochemical as well as histopathological consideration.

**Results:** Butin pretreatment significantly attenuated D-GalN-induced hepatocytes damage by reducing hepatic markers and its ability in attenuating oxidative damage (MDA, GSH, SOD, CAT) and pro-inflammatory cytokine (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) and MPO. Histopathological assessment of liver and biochemical estimation confirmed the hepatoprotective effects of butin. **Conclusions:** These results demonstrated butin protect experimental rats against D-GalN-induced liver injury by modulating lipid peroxidation and pro-inflammatory cytokine. Current research will give preliminary experimental evidence for butin, possible therapeutic effects in liver disorders.

**Keywords:** Butin, D-galactosamine, experimental design, hepatoprotective activity

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*by S N*

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## 1. Introduction

Liver injury is a threatening disorder that poses significant clinical problems with a 30% mortality rate (Stravitz and Lee 2019). Hepatic impairment occurs rapidly, leading to progressive multiorgan failure and hepatic encephalopathy. Viruses, drug-induced liver damage, alcoholic hepatitis, cryptogenic liver failure, and pregnancy-related acute liver disease are the most prevalent reason for liver damage (Marrone et al., 2021). Hepatotoxic substances react with liver cell components, resulting in a variety of liver ailments. Chemical poisons including galactosamine, acetaminophen, thioacetamide, and carbon tetrachloride have been successfully utilized in earlier to establish <sup>29</sup> *in vitro* and *in vivo* models of experimental hepatocyte injury (Tsai et al., 2021). D-Galactosamine (D-GalN), which is generated from D-galactose, is a renowned hepatotoxic drug that causes a diffuse kind of liver injury with necrosis, inflammation, and regeneration that is morphologically and functionally comparable to human viral hepatitis (Chen et al., 2021). In animal models of liver injury, D-GalN is often employed due to its great repeatability and ease of dosage management. D-GalN inhibits the hepatocyte RNA synthesis and lowers the quantity of cellular uridine-5'-triphosphate (UTP) to impede transcription in the liver (Park et al., 2020).

The flavonoid butin can be obtained from a variety of medicinal plants, including *Rhus verniciflua* Stokes, *Parkinsonia aculeata* L, *Vernonia anthelmintica* Willd, *Dalbergia odorifera* and *Adenantha pavanina* (Su <sup>3</sup> et al., 2007, Chen et al., 2016, Abdelaziz et al., 2020). Butin has been shown to be a influential antioxidant in the treatment of stress-induced illnesses such as liver disease, diabetes and cancer <sup>12</sup> (Brusselmans et al., 2005, Kuzu et al., 2008, Shu et al., 2009). Butin reduces apoptosis and the inflammatory response in intracerebral hemorrhage (ICH) rats, which alleviates the altered behaviour and neuronal state <sup>27</sup> (Li and Jiwu 2018). Butin has previously been revealed to defend cells and activating antioxidant enzymes by apoptosis triggered by hydrogen peroxide by scavenging reactive oxygen species (ROS) (Zhang et al., 2008). Butin has anti-myocardial I/R properties. The cardioprotection in setting of diabetes by butin is likely mediated through activation of AMPK/Akt and GSK-3/Nrf2 signalling pathways (Duan et al., 2017). Butin has been shown to provide a successful response in a hydroquinone-

induced experimental vitiligo model, and its putative tools include increased tyrosinase-related protein-1 (TRP-1) and tyrosinase (TYR) expression and decreased cholinesterase (CHE) activity as well as malondialdehyde (MDA) (Huo et al., 2017). Despite the fact that butin reported anti-inflammatory, antioxidant, anti-apoptic, antiplatelet, skin whitening and anti-implantation effects (Chen et al., 2016). Hepatoprotective impact of butin in the context of liver damage caused by D-GalN has never been investigated. As a result, the goal of this work was to investigate butin produce hepatoprotective properties and underlying mechanisms against D-GalN-produced liver toxicity via lipid peroxidation and pro-inflammatory cytokine modulation.

## 2. Methods

### 2.1. Experimentation

Male Wistar rats weighing 150 to 200 gm and aged 10 to 12 weeks were used. Animals were randomly divided into groups, each with six animals. Before the experiments, the experimental rats were given free access to a normal diet as well as unlimited access to tap water *adlibitum*. Animal Ethics Committee of the Institution agreed the protocol, and adheres to the CPCSEA, Government of India (IAEC/918/CPCSEA/01).

### 2.2. Chemicals

D-GalN and Butin was obtained from Sigma Aldrich (USA). The rest of reagents and chemicals used were high-quality.

### 2.3. Experimental research model and D-GalN-induced hepatoprotective treatment protocol

The following treatments were administered to 24 rats equally divided into four groups. Group I: preserved as normal for a 21-day study period, with distilled water at a rate of 1 ml/kg. Group II: D-GalN control treated with a D-GalN 400 mg/kg intraperitoneal single dose on the 21<sup>st</sup> day to produced hepatotoxicity (Raish et al., 2016). Groups III and IV: Butin 25 and Butin 50 mg/kg group was administered for a period of 21<sup>st</sup> days and challenged with a singly D-GalN dose at 400 mg/kg/i.p. on the day of 21<sup>st</sup>. Biochemical and histopathological assessment was performed on 22<sup>nd</sup> days.

## 2.4. Evaluation parameters

### 2.4.1. Biomarkers estimation

Biomarkers like aspartate aminotransferase (AST) (Frankel and Meyer 2000), alanine aminotransferase (ALT), alkaline phosphatase (ALP) (Goodla et al., 2017), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) (Adewale et al., 2019), total protein (TP) (Gornall et al., 1949), albumin (GRANT 1987) and total bilirubin (TB) (Gupta et al., 2005) and were assessed. The liver specimens were extracted and homogenates (10% w/v). The resulting supernatant was utilised to determine catalase (CAT)(Aebi 1984), glutathione peroxidase (GSH) (Sedlak and Lindsay 1968), superoxide dismutase (SOD)(Nandi and Chatterjee 1988),  $\gamma$ -glutamyl transferase (GGT) (Persijn and van der Slik 1976) myeloperoxidase (MPO) (Van Dielen et al., 2004) and lipid peroxidation (malondialdehyde-MDA)(Ohkawa et al., 1979).

### 2.4.2. Measurement of TNF- $\alpha$ , IL-1 $\beta$ and IL-6 in serum

The IL-6, IL-1 $\beta$  and TNF- $\alpha$  serum concentration were quantified by immunoassay kit.(Chen et al., 2016).

### 2.4.3. Histopathological estimation

Experiments ended with the animals being sacrificed. In order to fix the liver tissue, a buffered neutral formalin solution of 10% was immediately used. The tissues were carefully embedded in molten paraffin with the help of metallic blocks, covered with flexible plastic moulds and kept under freezing plates to allow the paraffin to solidify. Cross sections (5 mm thick) of the fixed tissues were cut. The microarchitecture of the tissues was observed under a light microscope using hematoxyline and eosin-stained sections. An investigator who was not aware of the biochemical results and treatment allocation performed the histological assessment (Shang et al., 2020).

## 2.5. Statistical analysis

Statistical correlation was accomplished by Prism software. The data are accessible as the  $\text{as mean} \pm$  S.E.M. One way ANOVA followed by post-hoc test (Tukey's),  $p < 0.05$  being considered as a significant difference.

### 3. Results

#### 3.1. Hepatic injury markers

D-GalN-induced liver damage (control group) caused substantial escalation in serum biomarkers ALT, ALP, AST, GGT and TB levels ( $p < 0.05$ ) as correlated to the normal. Conversely, treatment with butin at different doses shows a considerable decline in the raised liver marker enzymes ALT, AST, ALP, as depicted in **Figure 1A-C**. In addition, butin with higher as well as lower doses substantially ( $p < 0.05$ ) abridged GGT levels and TB content in treatment group (**Figure 1D and 2A**). TP levels were noticeably ( $p < 0.05$ ) reduced in D-GalN-induced rats correlated with normal, whereas in the butin treated group were appreciably improved ( $p < 0.001$ ) (**Figure 2B**). D-GalN-induced rats albumin levels were substantially higher than those of normal (**Figure 2C**). Compared to D-GalN group rats, butin significantly restored the elevated albumin levels ( $p < 0.05$ ,  $p < 0.001$ ).

#### 3.2. Oxidative markers

**Figure 2D** demonstrates the substantial ( $p < 0.05$ ) gain in the MDA (lipid peroxidation) in the D-GalN-induced rats. Butin treatment on the other hand, considerably ( $p < 0.001$ ) reduced lipid peroxidation than the D-GalN group.

#### 3.3. Endogenous antioxidant enzyme markers

The hepatic GSH, SOD, CAT level was remarkably reduced in the D-GalN-control ( $p < 0.05$ ) than the normal (**Figure 3A-C**). Treatment with butin (25, 50 mg/kg) restored endogenous antioxidant enzyme-GSH, SOD, CAT activities in treatment group ( $p < 0.001$ ).

#### 3.4. Pro inflammatory cytokines and MPO markers

The TNF- $\alpha$ , IL-1 $\beta$ , IL-6-pro-inflammatory cytokines were all dramatically upregulated the activity of pro-inflammatory factors in response to D-GalN challenge. Butin (25, 50 mg/kg) with lower-higher dose effectively prevented the increase TNF- $\alpha$ , IL-1 $\beta$  and IL-6 levels (Figure 4A-D). MPO activity was significantly higher in D-GalN- control. However, treatment with butin significantly ( $P < 0.001$ ) improved the MPO level produced by a D-GalN in treatment group.

### 3.5. Lipid profile

The TC and TG were significantly increased, whereas the HDL was substantially ( $p < 0.05$ ) reduced by D-GalN as correlated with normal. In treatment groups (Butin 25, 50 mg/kg) TC and TG were suggestively reduced ( $p < 0.001$ ) as correlated to D-GalN animals. Interestingly, pre-treatment of rats with butin ( $p < 0.001$ ) improvement in these abnormalities, as shown in Figure 5A-C. Butin treated rats favorably modulated lipid parameters.

### 3.6. Changes of hepatic tissue

Rats with normal hepatocyte architecture were observed in a photomicrograph of the liver in normal. (Figure 6 A). In difference, the liver cells of D-GalN control group rats exhibited massive coagulative necrosis, hemorrhage, inflammation and central vein congestion as associated to normal group (Figure 6B). Butin (25 mg/kg) lower dose pretreated induced D-GalN, there was mild inflammation and moderate tissue necrosis histoarchitecture of liver sections of butin (50 mg/kg) demonstrated a progress in the pathological characteristics, including mild inflammation. All these results suggest that pretreatment with butin prior to D-GalN injection provides defensive measures in rats (Figure 6C and D).

## 4. Discussion

The liver is a metabolically active organ that is in charge of biotransformation and clearance of xenobiotic from the body. It is a popular target for medications and pathogens, which can harm liver cells and decrease general liver function, leading to hepatitis, cirrhosis, and hepatocellular carcinoma. Unfortunately, clinically effective pharmacological treatments for hepatic illness are still desperately desirable (Dong et al., 2020). D-GalN-induced hepatic damage is a well-known method of xenobiotic-



induced hepatotoxicity that is commonly used to identify anti-hepatotoxic or hepatoprotective agents. A rising body of supports recommended that stress and the inflammation are both linked to the enlargement of hepatic damage and have a part in the disease pathogenesis (Hu et al., 2020). As a result, medicines that can improve liver functions, act as antioxidants and anti-inflammation properties could be evaluated as viable therapeutic approaches for liver injury.

The purpose of experimental was to gain an enhanced perceptive of the action underlying D-GalN-produced liver damage and investigate the influence of butin on D-GalN-produced hepatic damage. The study confirmed the hepatoprotective effects of butin in rats challenged with D-GalN. The ALT, GGT, AST and ALP are directly implicated key biomarkers in hepatic injury and indicate the rigor of D-GalN impairment. This study found that giving D-GalN to rats caused a considerable rise in ALT, ALP, AST and GGT as well as increased inflammatory infiltration, massive coagulative necrosis, hemorrhage and central vein congestion as well as a deterioration of hepatic integrity, which is in accordance with prior findings (Rouf et al., 2021). The hepatic cell membrane permeability is disrupted by D-GalN injection, leading in hepatic enzyme loss from the cell and an increase serum enzyme. In addition, excess reactive free radicals formed by D-GalN change the antioxidant prominence of some organs, rendering them further liable to stress (Prakash et al., 2018). As a result, the current *in vivo* study may be appropriate for assessing hepatoprotective drugs. It is possible that pre-treatment of butin reduces hepatic injuries by preventing ionic pump dysfunction, cell leakage, and membrane damage. Serum TB, on the contrary, is a well-known functional hepatic marker linked to hepatic and biliary disorders, as well as acute disturbance of hepatocellular structural design and function, greater serum TB levels are commonly detected in D-GalN-induced liver damage. However, butin treatment appreciably attenuated the deleterious effects of TB. To assess noxious effects of toxicants, TP, albumin levels can be used. Proteins are synthesized most efficiently in hepatocytes. The equilibrium of synthesis, use and breakdown is reflected in plasma protein levels. Severe hepatic damage has been linked to a decrease in the production of various protein (Rouf et al., 2021). Butin showed protective effects on total protein and albumin. This findings are agreement with

that of the Prakash *et al.* (2018) (Prakash et al., 2018). Butin may be exhibited hepatoprotective effects based on histopathological and biochemical studies. Butin could considerably diminish the biomarkers expression of stress while mounting the activity of anti-oxidant enzymes. Meanwhile, cytokines, which are important controllers of inflammation in hepatic impairment, may be suppressed by butin treatment. Butin scavenged activating endogenous antioxidant enzymes and ROS to diminish stress-induced mitochondrial dysfunction, declined stress-induced 8-hydroxy-2'-deoxyguanosine levels by activating oxoguanine glycosylase 1, protected cells against apoptosis triggered by hydrogen peroxide (Zhang et al., 2008). The intracellular organelles that produce the most ROS in cells are crucial in the advance of oxidative stress in normal and pathological sittings and mitochondrial malfunction is mainly probable triggered oxidative stress-induced apoptosis. Lipid peroxidation is a well-known stress and cell injury mechanistic pathway. The stress caused by D-GalN- accumulates hepatic lipid peroxides and depletes antioxidant enzymes such as CAT, GSH and SOD. Butin reduced the toxic effects of D-GalN by suggestively dropping lipid peroxidation. Butin inhibitory impact on lipid peroxidation suggested that it could protect the liver from free radical-induced injury and consequent pathological alterations.

Antioxidant enzymes, such as SOD, are crucial antioxidant defense systems that protect the body from ROS. SOD has the capacity to alter SOD radicals to hydrogen peroxide, which can then be catalysed by GSH-px to produce water and oxygen (Han et al., 2020). The treatments with butin also showed a restored GSH, SOD, and CAT levels. Hence, natural flavonoids are proving to be effective treatments for diseases caused by free radicals.

MPO was not only thought to be a neutrophil marker, but it could also make hypochlorite from hydrogen peroxide and chloride ions, resulting in free radicals that could cause oxidative stress and tissue damage (Chen et al., 2020). Butin significantly decreased levels of MPO in a D-GalN-treated model according to our finding. When D-GalN causes liver damage, it increases cytokines expression, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 and generates ROS, which triggers a downstream signaling cascade (Lv et al., 2017). Furthermore, butin may reduce the cytokines expression, which are important controllers of

inflammation in liver injury. D-GalN significantly improved the TNF- $\alpha$  level in this study. TNF- $\alpha$  is the most important pleiotropic cytokine, capable of initiating an inflammatory cascade that leads to the production of other cytokines, such as IL-1 $\beta$ , IL-6. Butin reduced the acute liver impairment induced by D-GalN by regulating inflammatory cytokines. Previous work demonstrated the pro-inflammatory modulatory effect of butin on ICH condition by changed NF- $\kappa$ B in the tissues brain (Trajkovska and Topuzovska 2017). Molecularly, cellular functions and homeostasis are regulated and maintained by lipids. Cholesterol, bile acid production, and phospholipid metabolism are the primary functions of the liver. Increased serum TG and TC levels, as well as lower HDL levels, are classic signs of liver injury, which matches our findings. When D-GalN-injected animals were compared to normal rats, we found a rise in serum TC and TG levels as well as a decrease in HDL levels, which is agreed with former outcomes (Mondal et al., 2020). As results of hepatocellular injury, a large amount TG accumulates in the parenchymal cells, which then discharge a substantial amount of TG into the bloodstream. Butin appears to have a protective effect produced D-GalN toxic effect, as seen by raise HDL and reduce in TC and TG. To summaries, the current study established the butin hepatoprotective efficacy in rats exposed to D-GalN-produced hepatic injury, including down-regulation of key factors such as MDA, GSH, SOD, CAT, MPO, IL-6, IL-1 $\beta$  and TNF- $\alpha$  which may be adequate to battle cellular damage. Butin may be protect hepatocytes and enhance liver tissue regeneration, according to histological recovery toward normalcy. However, more research is needed to corroborate these findings and to establish butin therapeutic benefits as a conventional hepatoprotective medication.

## 5. Conclusion

This study examines butin ability to protect the D-GalN-induced liver damage. The D-GalN prompted hepatic toxicity (elevated in hepatic markers, amplified oxidative stress, and decreased antioxidants and increased proinflammatory markers) was ameliorated by pretreatment of butin. These findings demonstrated butin protective effects against rats challenged with D-GalN-induced liver impairment by modulating pro-inflammatory cytokine and lipid peroxidation as well as buildup, as demonstrated by the

clear morphology of liver cells. The current research will give preliminary experimental evidence for butin, possible therapeutic effects in liver syndromes.

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#### **Disclosure statement**

The authors declare no conflict of interest

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