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Research Article

The Potential Effect of Silymarin Against Paracetamol-Induced Hepatotoxicity in Male Albino Rats

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ABSTRACT

Background: Being the main metabolic organ, liver stays in touch with toxicity of introduced materials including, drugs. Protection is priceless to avoid complication of liver toxicity. **Objectives:** This research aimed to assess the protective impact of silymarin (SIL) on hepatotoxicity based on acute paracetamol (APAP) intoxication in rats in comparison with N-acetylcysteine (NAC). **Methods:** To do so serum was collected and the liver was analyzed for histological findings on rat model-paracetamol toxicity whether alone or in combination with SIL or NAC. The scenario was based on either preconditioning with SIL/NAC before induction of toxicity or afterwards. Serum liver function tests, pro-oxidant/antioxidant status, and proinflammatory markers were detected alongside liver histological study. **Results:** The results showed that liver function indices, oxidative state, and pro-inflammatory parameters were significantly changed, and histopathological alterations were detected in the liver of the intoxicated group. These modifications were inverted in groups treated with either SIL or NAC. The results of the current study suggested that SIL might be employed as a hepatoprotective drug against liver damage induced by APAP because of its ability to reduce lipid peroxidation, improve antioxidant defense status, and have anti-inflammatory effects. **Conclusion:** These results are equivalent to NAC therapy which is a standard drug against APAP-related hepatotoxicity.

Key words: Hepatotoxicity, NAC, APAP, Silymarin, Paracetamol, TNF-α.

INTRODUCTION

The liver plays a crucial role in a variety of physiological processes. These include the control of blood volume, immune system preservation, endocrine control of growth signaling pathways, and assistance with the metabolism of numerous substances.[1] Since it plays an important part in the metabolism of many pharmaceuticals as well as many endogenous and exogenous chemicals, liver tissue damage is frequently linked to the use of many medications.[2] An essential phenomenon in the development of homeostasis is the detoxification of pharmaceuticals and xenobiotics by drug-metabolizing enzymes in the liver. A change in homeostasis causes a shift in the metabolism's dynamic balance toward the production of reactive oxygen species (ROS), which causes oxidative stress and organ dysfunction.[3]

Paracetamol (synonym acetaminophen, APAP), when administered in typical therapeutic quantities, it possesses anti-inflammatory, analgesic, and antipyretic effects. It's readily available and suitable for people of all ages. The temptation to take it in large dosages for faster benefits is the major source of worry since it increases the risk of acute liver failure, which can be life-threatening and sometimes need liver transplantation.[2]

At the appropriate therapeutic APAP doses, APAP is mostly metabolized in the liver to excretable metabolites which are glucuronide and sulfate conjugates.[4] A small amount of the APAP dosage is oxidized by the cytochrome P450 (CYP450) enzyme system in the liver to the reactive toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified almost instantly by reduced glutathione (GSH) and eliminated through all the biliary or renal systems. Paracetamol at large doses enables the glucuronidation and sulfation pathways to become saturated, leading to GSH depletion with increased NAPQI concentration, which produces severe oxidative stress, mitochondrial malfunction, an inflammatory response, and even cell death.[5,6] The two prominent mechanisms in APAP-related hepatotoxicity are the covalent binding of NAPQI to hepatocytes in addition to oxidative stress and lipid peroxidation (LPO).[7] Furthermore, excessive NAPQI synthesis causes the pro-inflammatory cytokines TNF-α and interleukin-1beta to be stimulated, reinforcing tissue necrosis.[8] Destruction of hepatocytes in turn results in the rise of serum level of aminotransferases such as ALT and AST as well as ALP, and gamma-glutamyl transferase (*γ-GT*), which are most commonly used markers in hepatotoxic studies.[9]

The established antidote for APAP intoxication is NAC, which may be taken orally or intravenously.[10] NAC is a sulfhydryl group-containing antioxidant that functions as a direct free radical scavenger, rises GSH production, and restores intracellular GSH levels that have been depleted by oxidative stress and inflammatory processes.[8] Certain therapeutic herbs such as *Silybum marianum*, generally known as milk thistle, have traditionally been used for the prevention and cure of hepatic disorders.[11,12] The active ingredient in milk thistle is SIL, a lipophilic extract derived from milk thistle seeds. It contains flavonolignan isomers, a flavonoid, and several additional components.[13] Silymarin's hepatoprotective properties can be explained by its antioxidant properties, which are due to the phenolic character of its flavonolignans.[14] Silybin is

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the principal physiologically active component of SIL and accounts for 50-70% of all flavonolignans isomers.[2,11] Silymarin's antioxidant activity is due to its capacity to operate as both a free radical scavenger and an LPO inhibitor, according to *in vitro* and *in vivo* studies.[15] Silymarin also protects the liver by acting as an antiviral, anti-inflammatory, antifibrotic properties and immunomodulator in the liver and immune cells.[13,16]

As NAC is the current antidote for the treatment of APAP-induced liver damage, a comparison of a promising antidote, such as silymarin, to NAC would be desired. The goal of this study is to see how effective SIL is in protecting rats from APAP-induced hepatotoxicity and to compare its efficacy with an established antidote such as NAC.

MATERIALS AND METHODS

Chemicals and reagents

Paracetamol 1000 mg tablet (from SANOFI, France) and NAC 600 mg capsules (from AMS ®, USA) were purchased from a local pharmacy in Mosul city. Silymarin 175 mg capsule was kindly gifted from 21st *Century® Healthcare*, *Inc*, USA. Other chemicals including thiobarbituric acid and trichloroacetic acid were supplied from Sigma Aldrich, USA. Assay kits for liver function tests: ALT, AST, and ALP were obtained from BIOLABS SA, Maizy, France. Total antioxidant capacity colourimetric assay kit and Rat specific TNF-α ELIZA kit were obtained from Elabscience Biotechnology, USA. The rest of the chemicals are utilized with analytical grade. All these parameters were measured according to the manufacturer's instructions provided with the kits.

Experimental animals

Adult male Albino rats [n=48, weight; (191-245g); aged (10-12 weeks)] were procured from the Animal House of the College of Veterinary Medicine / University of Mosul. Before beginning the experiment, the animals were kept in metallic cages and given a two-week adaptation period in the lab. settings, which included a 12-hour light/dark cycle, a temperature of 25°C±5, humidity level of 45-50%. The animals were given unrestricted access to chow and water. The study was carried out with the approval of the Veterinary Medicine Department's Institutional Animal Care and Use Committee at the University of Mosul in Iraq. Ref: UM.VET.2021.30.

Blood collection and excision of liver

The research study's rats were weighed individually after 24 hours from the last dose was dispensed (day 8), and blood samples were then taken by promptly puncturing each rat's retro-orbital plexus with a capillary tube. Clear serum samples were transferred into clean Eppendorf tubes and stored at -20°C for subsequent biochemical analysis after blood were collected into clean plain tubes and allowed to clot for 45 minutes. Liver tissues were swiftly taken from animals after blood sample and cleaned with cold saline before specimens (small pieces from each liver) were transferred into 10% formalin for histological analysis. Animals were then killed by cervical displacement.

Histopathological assessment

The fixed tissue samples in 10% formalin were dehydrated and cleared before being embedded in paraffin wax and sectioned into 5µm thick sections. Tissues were stained with hematoxylin and eosin (H&E) and viewed under a light microscope to detect any pathological signs of toxicity.

Statistical analysis

The data were analysed by SPSS (V. 23) software. Data expressed as mean±SD. Differences between all groups were assessed with a One-way Analysis of Variance test (ANOVA-test) followed by a post-hoc-Tukey multiple comparison test. P values less than 0.05 considered significant.

RESULTS

Biochemical results

Analysis of liver enzymes profile

Acute APAP 2000 mg/kg oral dose produced a highly significant elevation in serum ALT, AST, and ALP activities ($p<0.01^{**}$) in comparison to the control group. However, post and pretreatment with SIL caused a noticeable reduction in these enzyme levels compared to the APAP group. Similarly, post and pretreatment with NAC exhibited a significant decline in enzymes level compared to the APAP group. The data were shown no significant variation between post-treatment with SIL and post-treatment with NAC. Moreover, no considerable change between pretreatment with SIL and pretreatment with NAC (Figure 1).

Serum total antioxidant capacity

The APAP group significantly decreased serum TAC levels compared to the control group ($P<0.01^{**}$). In comparison to the APAP group, both post and pretreatment with SIL display a significant increase. Similarly, post and pretreatment with NAC produce a highly significant elevation. The post-treatment with SIL displays no significant change with post-treatment with NAC. Furthermore, pretreatment with SIL displays no considerable change with pretreatment with NAC (Figure 2).

Serum malondialdehyde concentrations

Malondialdehyde serum levels raised substantially in the APAP group ($p<0.01^{**}$) compared to the control group. Silymarin post and pretreatment produced a highly significant decline compared to APAP intoxicated group. Also, N-acetylcysteine post and pretreatment revealed a noticeable decrease compared to APAP intoxicated group. No difference between the post-SIL and post-NAC supplementation is detectable. Meanwhile, pretreatment with SIL exhibits no appreciable difference from pretreatment with NAC (Figure 3A).

Analysis of serum tumor necrosis factor-alpha

In comparison to the control group, the APAP group resulted in a substantial increase in serum TNF- levels ($P<0.01^{**}$). When compared to the APAP group, both post and pretreatment with SIL indicate a significant decrease. Additionally, both post and pretreatment with NAC result in a highly significant reduction. There's also no major difference between SIL and NAC post-treatments. Furthermore, there is no significant variance between SIL and NAC pretreatments (Figure 3B).

Evaluation of the histopathology of liver sections

The histological observations of liver tissues performed by this study demonstrated the control group and the groups that were treated with SIL and NAC only which showed normal lobular histo-architecture, normal hepatocytes, intact cytoplasm, well-defined sinusoids, and Kupffer cells. Acute oral induction of hepatotoxicity by APAP were produce histopathological changes characterized by severe necrosis, inflammation, and the presence of haemorrhage. The presence of cellular necrosis, haemorrhage, and inflammation due to APAP intoxication diminished markedly when paracetamol was combined with either SIL or NAC (Figure 4). More details of the histological analysis are outlined in table 1.

DISCUSSION

The efficacy of SIL to prevent or cure liver damage and oxidative stress investigated by an oral acute high dosage of APAP in rats is investigated in this experimental investigation and their effect is compared to NAC.

Table 1: Liver histological findings of studied groups.

Group	Main histological findings
Control	-Typical liver histology with central vein, hepatocytes, and Kupffer cells
APAP	-Cellular debris of necrotic hepatocytes sloughing and desquamating surrounding blood vessels, whereas other hepatocytes had pyknotic nuclei -Hemorrhages plus extensive dispersion of lymphocytes between necrotic hepatocytes -Coagulative necrosis surround blood vessels, infiltration of lymphocytes, and macrophages
SIL	-Healthy histological features with central vein, hepatocytes, and Kupffer cells
NAC	-Normal liver architecture with central vein, hepatocytes and Kupffer cells
APAP+SIL	-Few necrotic hepatocytes -Infiltration of macrophages surrounding the portal region -Mild haemorrhages alongside normal hepatocytes
SIL+APAP	-Few necrotic hepatocytes around the portal location
APAP+NAC	-Interstitial haemorrhages surrounding the central veins -Hepatocytes have vacuolar degeneration around the portal area
NAC+APAP	-Few necrotic hepatocytes nearby the portal area -Interstitial haemorrhages between hepatocytes

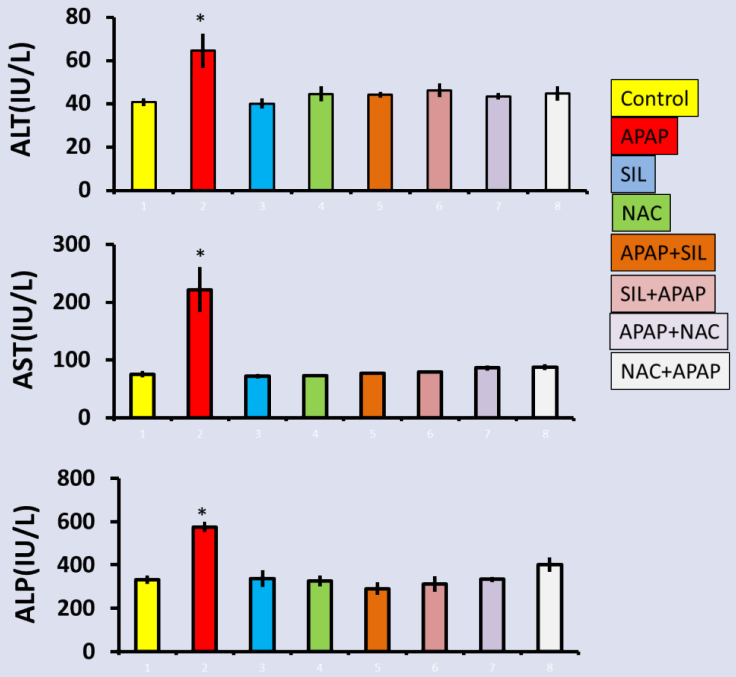

Figure 1: Modulation in liver function test in tested groups (n=6 each). Analysis obtained by One-way ANOVA test followed by Tukey's multiple comparison test. Data expressed as mean±SD, *p<0.05 as compared to the APAP group. TAC=total antioxidant capacity, APAP=paracetamol, SIL=silymarin, and NAC=n-acetylcysteine.

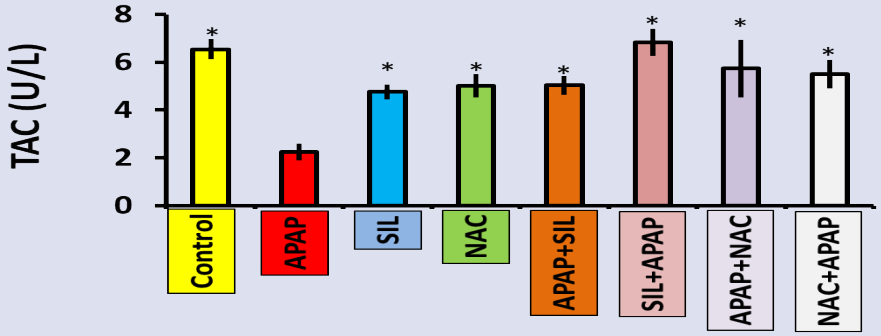

Figure 2: Total antioxidant capacity of studied groups (n=6 each). Analysis obtained by One-way ANOVA test followed by Tukey's multiple comparison test. Data expressed as mean±SD, *p<0.05 as compared to the APAP group. TAC=total antioxidant capacity, APAP=paracetamol, SIL=silymarin, and NAC=n-acetylcysteine.

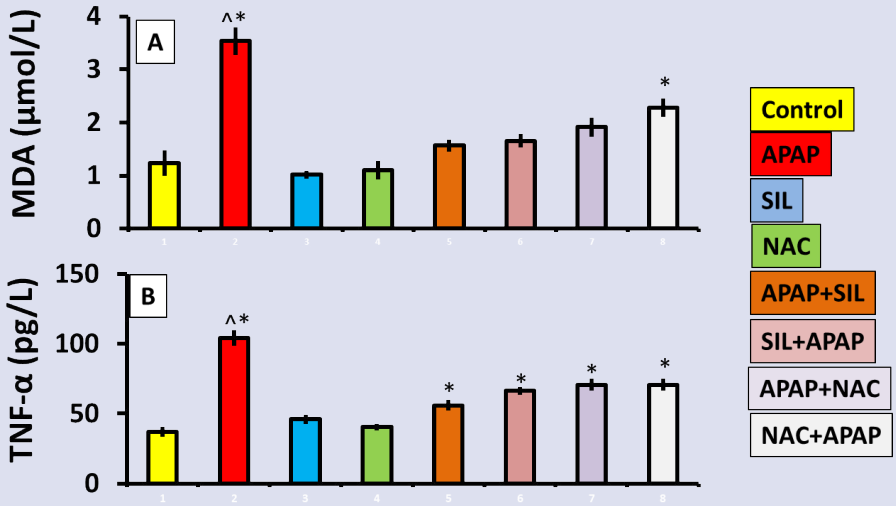

Figure 3: Pro-oxidant/proinflammatory capacity of studied groups (n=6 each). Analysis obtained by One-way ANOVA test followed by Tukey's multiple comparison test. Data expressed as mean±SD, *p<0.05 as compared to the control group. ^p<0.05 as compared to all other groups TAC=total antioxidant capacity, APAP=paracetamol, SIL=silymarin, and NAC=n-acetylcysteine.

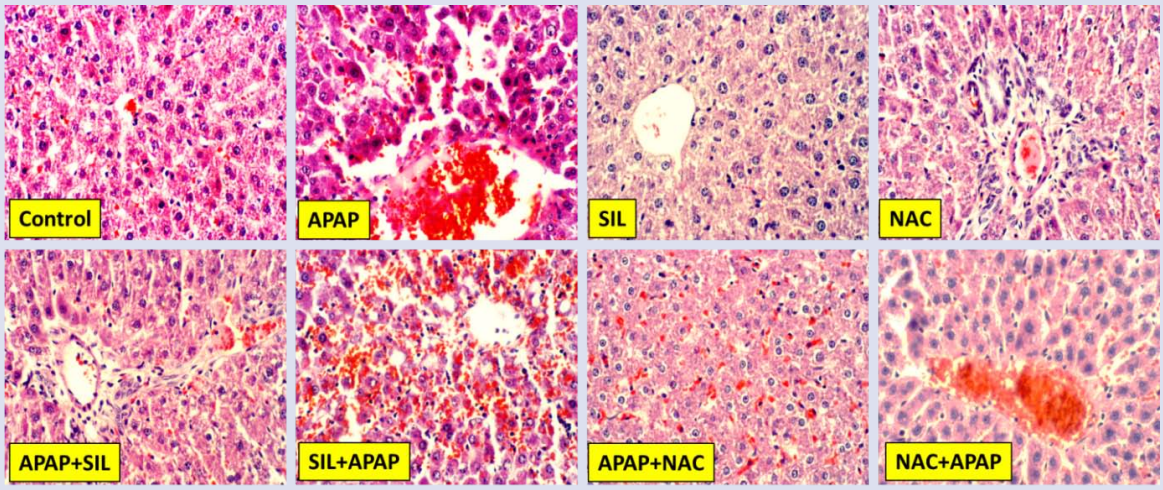

Figure 4: A representative image for liver histology of studied groups. Liver slices stained with H&E, X400.

This study unequivocally established that APAP intoxication resulted in a considerable escalation of blood levels of liver damage indicators, oxidative status alterations, the activation of an inflammatory response, and histopathological changes in liver sections. However, the use of SIL or NAC decreased the worsening of histoarchitecture as well as biochemical abnormalities.

By measuring several intracellular enzymes like ALT, AST, and ALP released into circulation through the hepatocyte membrane, we determined the level of drug-induced hepatotoxicity. Serum ALT, AST, and ALP levels that are higher than normal are signs of cellular leaking and a breakdown of the functional integrity of the liver cell membrane.[17,18] Alanine aminotransferase is a cytoplasmic enzyme that may easily leak into the blood after hepatocyte membrane disruption, making it a more sensitive and specific biomarker of liver injury than AST. Aspartate aminotransferase levels show liver damage that involves the mitochondrial organelles, such as viral hepatitis and other pathologic diseases, whereas ALP provides information relating to the activity of hepatocytes. Increased ALP synthesis in response to rising biliary pressure may be the cause of the elevated ALP serum level.[17-20]

In the present study, a tested acute oral APAP dose is capable to elevate ALT, AST, and ALP activities in the blood (significant elevation) compared to the control animals group, which may be an indication of liver damage and cell necrosis resulting from the formation of NAPQI over GSH detoxification capacity.[17,19] A few earlier studies have shown the same findings.[7,21-23]

Milk thistle extract, or SIL, is a widely used phytochemical that herbalists throughout the world recommend to keep the liver healthy.[24] Numerous studies reveal that SIL has powerful antioxidant effects and protects against liver toxicity brought on by a wide variety of substances by inhibiting LPO.[13,15,25] Silymarin's antioxidant activity and associated hepatoprotective benefits are attributed to the phenolic component of this extract.[14,25] These findings support our findings about the hepatoprotective effects of SIL. In this investigation, SIL significantly reduced the activity of ALT, AST, and ALP serum levels compared to the APAP group. This result might be due to SIL's ability to reduce APAP damage and restore normal hepatocyte integrity by combating ROS.[7,18,25-27] Similarly, NAC treatment significantly inhibits the rise in ALT, AST, and ALP as compared to the APAP intoxicated animals.[28-30]

Post and pretreatment with SIL attenuate the oxidative stress as indicated by a decrease in serum MDA and an increase in serum TAC relative to an intoxicated group. These implications may be caused by SIL's capacity to directly hunt free radicals created during hepatic APAP metabolism, inhibit free radical formation, maintain the mitochondria's electron-transport chain integrity under stress situations, and promote optimal redox homeostasis of the cell by activating a variety of antioxidant enzymes and non-enzymatic antioxidants, raising cellular glutathione levels, and inhibiting LPO.[7,13,31] Our results are in line with earlier research.[32,33] N-acetylcysteine has been shown antioxidant effects by free radical scavenging and acts as a source of sulfhydryl moiety, consequently promoting GSH biosynthesis. Hence our observation indicates NAC treatment, significantly reduces serum MDA levels as shown in previous reports.[34,35] Moreover, serum TAC levels significantly increased, which was likewise consistent with earlier observation.[36]

Oxidative stress and inflammatory cascade response are related.[26] Macrophages create tumour necrosis factor-alpha in reaction to tissue injury.[8] Following APAP overdose, pathological alterations can be brought on by tumour necrosis factor-alpha and other pro-inflammatory cytokines,[2] which was also seen in our investigation. Overdosing on acetaminophen dramatically raises serum TNF- levels. This result is consistent with earlier studies.[5,37]

In the present study SIL treatment significantly alleviate the production of pro-inflammatory TNF-α compared with the hepatotoxic group. This result is in agreement with prior studies.[5,26,31] These findings imply that SIL may reduce liver damage brought on by APAP by reducing the inflammatory response.[27] N-acetylcysteine treatment significantly attenuates the production of TNF-α, as early detected, due to its anti-inflammatory effects and decreases excessive production of TNF-α and expression of inflammatory mediators.[29]

Histopathological changes in liver histoarchitecture provided substantial support for the serum biochemical results that were previously described. The representative derangement in liver architecture observed in APAP intoxicated animals.[38,39] was improved in animals treated with either SIL or NAC. Silymarin exhibits considerable regeneration activity and fewer disorganized hepatocytes, which are almost identical to the normal hepatic architecture.[37,38,24] Likewise, N-acetylcysteine treatment revealed marked regeneration and improvement in hepatocytes, near the normal histologic architecture.[8,40,27,36]

CONCLUSION

In summary, our research showed that standardized milk thistle extract, or SIL, might act as a shield for rats' livers against acute hepatic damage caused by large doses of APAP. In a way similar to well-known hepatic defender NAC. Post and pretreatment with SIL dramatically reduced serum levels of hepatic damage markers, a pro-inflammatory cytokine, and improved oxidative status as well as histological modification. Silymarin's anti-oxidative and anti-inflammatory qualities cause it to have hepatoprotective effects.

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CONFLICTS OF INTEREST

No conflicting interests are disclosed by the authors.

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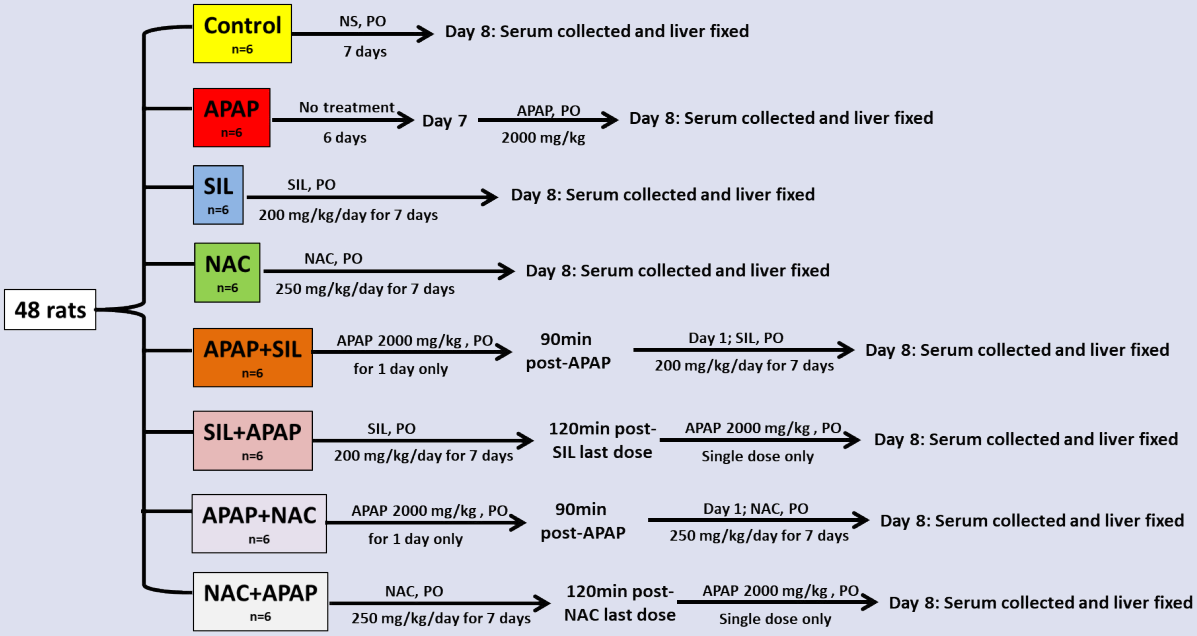
GRAPHICAL ABSTRACT



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