

# CAN RUTIN BE USED AS AN ANTIDOTE FOR ACUTE ACETAMINOPHEN INDUCED HEPATIC TOXICITY? AN EXPERIMENTAL STUDY

*BY*

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## ABSTRACT

*Acetaminophen (APAP) is the most commonly reported toxic ingestion in the world. Severe liver injury resulting from overdose of APAP remains a significant clinical problem. This study aimed to assess the use of rutin in the treatment of acute acetaminophen toxicity compared to N-acetyl cysteine (NAC) in mice. Sixty mice were divided into 6 groups; group (1) as a control group, group (2) was given toxic dose of acetaminophen 250 mg/kg once by intraperitoneal injection "i.p.", group (3) was given N-acetyl cysteine 204 mg/kg once i.p., group (4) was given 28 mg/kg rutin once orally, group (5) was given toxic dose of acetaminophen followed by N-acetyl cysteine after one hour once i.p. and group (6) was given toxic dose of acetaminophen followed after one hour by four oral doses of rutin at 12 h intervals. Animals were sacrificed 12h after the last treatment. Alanine transaminase (ALT) was measured and liver was removed and examined histopathologically. Results showed that acute acetaminophen hepatotoxicity was best treated by multiple doses of rutin rather than single dose of NAC. It is concluded that rutin can be used in treatment of acetaminophen induced acute hepatic toxicity.*

**Keywords:** acetaminophen, mice, rutin, N-acetyl cysteine, hepatotoxicity

## INTRODUCTION

Acetaminophen (Paracetamol, N-acetyl-P-aminophenol (APAP)) is one of the most widely used analgesic antipyretics worldwide. It is one of the most common pharmaceuticals associated with both intentional and accidental poisonings (Ray et al., 1996).

The role of N-acetylcysteine (NAC) in treatment of acetaminophen overdose is well established (Rumack, 2002). It mainly acts by providing cysteine, a precursor for glutathione (GSH) synthesis, thus enhancing metabolism of N-acetyl-P-benzoquinoneimine (NAPQI), a toxic metabolite of APAP, so reducing hepatotoxicity induced by toxic doses of APAP (Cor-

coran and Wong, 1986).

Rutin is one of the phenolic compounds and flavonoid glycosides mainly found in flowers and fruits. It was first extracted from *Ruta graveolens* which is broadly spread in nature (Lee and Jeune, 2013). Rutin, exhibits multiple pharmacological activities including anti-bacterial, anti-viral (Panasiak et al., 1989), anti-protozoal (Iwu et al., 1986), anti-tumor (Deschner et al., 1991), anti-allergic (Chen et al., 2000), anti-inflammatory (Aleksandrov et al., 1986) and anti-platelet (Swies et al., 1984) activities.

Moreover, anti-diarrheal (Di-Carlo et al., 1993), anti-ulcer (La Casa et al., 2000), anti-spasmodic (Mata et al., 1997), anti-mutagenic (Bear and Teel, 2000), myocardial protecting (Pozin et al., 1996), vasodilator (Chung et al., 1993) and anti-oxidant (Kamalakkannan and Prince, 2006) activities of rutin have also been reported. It has been traditionally used in liver damage (Perry, 1980). Pre-treatment of rats with rutin prevented both paracetamol and CCl<sub>4</sub> induced rise in hepatic enzymes (Janbaz et al., 2002).

The aim of this work is to assess the possibility of using rutin as an antidote for acute acetaminophen toxicity compared to N-acetylcysteine therapy in mice.

## **MATERIAL & METHODS**

### **Chemicals :**

Injectimol infusion bottle (100 ml) (Acetaminophen, N-acetyl-P-aminophenol (APAP) parenteral solution as 10 mg/ml, El-Amreia Co.) was purchased from the local market and used for intraperitoneal injection (i.p.) injection. Rutin (Sigma) was dissolved in distilled water forming emulsion and was given orally by gavage. N-acetylcysteine (Sedico Co.) was dissolved in saline and used as i.p. injection.

### **Animals:**

Sixty Balb C male mice (25–30 g) obtained from Medical Experimental Research Center (MERC), Faculty of Medicine, Mansoura University were used in this study. Animals were housed under standard environmental conditions and had free access to tap water and food.

### **Study design:**

Mice were divided into 6 groups, 10 mice each. Group (1) served as control group. Group (2) was given toxic dose of acetaminophen (250 mg/kg once by intraperitoneal injection "i.p.") according to Terneus et al. (2008). Although intraperitoneal route is not the usual route of exposure, it was chosen being easier besides the aim was induction of hepatotoxicity through i.p. route as previously reported by Terneus et al. (2008). Group (3) was given N-acetyl cysteine in a dose of 204

mg/kg once i.p. (Terneus et al., 2008). Group (4) was given rutin once orally according to the study of Janbaz et al. (2002) on rats, the dose was calculated in mice by using Paget and Barnes table and was found to be 28 mg/kg. Group (5) was given toxic dose of acetaminophen followed by N-acetyl cysteine after one hour once ip. Group (6) was given toxic dose of acetaminophen followed after one hour by four oral doses of rutin received at 12 hours intervals till the end of 48 hours. All animals were sacrificed by cervical dislocation 12 hours after the last treatment.

#### **Methods:**

Blood sample was collected from each animal for determination of alanine transaminase (ALT) as a liver function test. Animals were dissected to obtain the liver to be examined histopathologically by the light microscope. Serum was separated by centrifugation of blood at 3,000 rpm for 15 minutes. Serum alanine transaminase (ALT) was estimated spectrophotometrically using Merck diagnostic kits.

Liver was removed from each animal, fixed in 10% of phosphate buffered (neutral) formalin, cleansed through running water, dehydrated by gradually increasing concentrations of alcohol, then extra alcohol was washed by xylene and embedded in paraffin block. The paraffin block was sectioned as 4~5  $\mu$ m thickness then it was stained with hematoxylin-

eosin and examined with a light microscope (Lica CX21 microscope). Liver sections then were scored and evaluated according to the severity of hepatic injury described by Ishak et al. (1995).

#### **Statistical analysis:**

Results were expressed as mean  $\pm$  SD, median and range. Data were processed using SPSS program Version 14. Statistical comparison between variables was made by the Student's t-test for ALT levels. Histopathological results were tabulated, and compared using Fisher Exact test.  $P < 0.05$  was regarded as significant.

### **RESULTS**

As shown in table (1), compared to negative control group, acute toxic dose of acetaminophen induced significant increase in ALT levels ( $P = 0.001$ ) meanwhile both rutin and NAC induced significant decrease in its levels ( $P = 0.022$  and  $0.034$  respectively). Administration of either rutin or NAC after acute toxic dose of acetaminophen improved ALT levels significantly in case of rutin ( $P = 0.008$ ) and insignificantly in case of NAC ( $P = 0.076$ ). However, in both groups ALT did not return to control level ( $P = 0.004$  and  $0.0001$  respectively). Rutin was better than NAC for improving ALT levels ( $P = 0.0001$ ).

Tabulation of histopathological score results is illustrated in table (2). Control

mice showed normal liver architecture (Fig.1) apart from minimal portal inflammation in 60 % of mice (Fig. 2). Both rutin and NAC groups showed normal liver architecture (Figs. 3 & 4 respectively).

Acetaminophen induced mild to moderate portal inflammatory reaction in 40% of mice and mild to moderate portal inflammatory reaction in all animals (100%) (Fig. 5), zone III (centrilobular) hepatocytes moderate degeneration, necrosis and apoptosis (Fig. 6) in 80% of mice and moderate hydropic degeneration (Fig. 7) in three out of the ten mice (30%). Macro and micro-vesicular steatosis (Fig. 8) was observed only in one mouse (10%).

Multiple doses of rutin improved toxic effects of acetaminophen on the liver of mice with some residual mild effects (Fig. 9) in the form of mild hydropic degeneration of zone I hepatocytes that was observed in five out of the ten mice (50%) and mild portal inflammation that was found only in one mouse (10%).

NAC also induced improvement of toxic effects of acetaminophen on the liver with some residual mild effects in the form of mild hydropic degeneration and mild portal inflammation (Fig. 10) in three out of the ten mice (30%).

Statistical comparison of pathological results (Table 3) showed that, compared to

control, acetaminophen induced insignificant ( $P = 0.133$ ) mild inflammatory reactions in zone I, significant moderate inflammatory reactions ( $P = 0.0001$ ) and moderate apoptosis ( $P = 0.0007$ ) in zone III of hepatic lobules. Multiple doses of rutin insignificantly ( $P1 = 1$ ) improved zone I inflammatory reactions but significantly improved zone I hydropic degeneration ( $P1 = 0.044$ ); inflammatory reactions ( $P1 = 0.0001$ ) and apoptosis ( $P1 = 0.0007$ ) in zone III of hepatic lobules. These improvements did not return to normal control figures for zone I hydropic degeneration ( $P = 0.032$ ) and inflammatory reactions ( $P = 0.057$ ).

On the other hand, NAC induced insignificant improvement in zone I hydropic degeneration ( $P1 = 0.23$ ) and inflammatory reactions ( $P1 = 0.60$ ). These improvements were insignificantly different from the control figures ( $P = 0.21$  regarding zone I hydropic degeneration and  $P = 0.37$  regarding inflammatory reactions). It induced significant improvement in zone III inflammatory reactions ( $P1 = 0.0001$ ) and apoptosis ( $P1 = 0.0007$ ).

Rutin and NAC were insignificantly different in improving acetaminophen induced zone I hydropic degeneration ( $P2 = 0.65$ ) and inflammatory reactions ( $P2 = 0.58$ ). Both rutin and NAC induced complete improvement of zone III inflammatory reactions and apoptosis.

## **DISCUSSION**

This study was conducted to assess the possible use of rutin as an antidote for acute acetaminophen toxicity compared to the current antidote N-acetylcysteine. Histopathological findings and serum ALT values observed in this study revealed that hepatotoxicity induced by acetaminophen overdose was best treated by multiple doses of rutin rather than the single dose of NAC; the standard regimen of acetaminophen overdose treatment.

High serum ALT levels in acetaminophen-treated mice were closely parallel to histopathological liver damage, as previously reported (Di Pierro and Rossoni, 2013; Kim et al., 2013; Yahya et al., 2013).

ALT levels obtained from the acetaminophen - rutin - treated mice were lower than those from the acetaminophen -NAC- treated mice. However, such values were significantly decreased compared to those of the acetaminophen group. Similar results were reported by Janbaz et al. (2002) who found that rutin pre-treatment could ameliorate acetaminophen induced hepato-cellular damage evidenced by preventing the increase of serum transaminases levels subsequent to its exposure. The advantage of the present study design is its simulation to clinical practice in that the antidotes were

used after exposure to a toxic dose of acetaminophen.

An interesting finding in the present study is the return of histopathological liver damage induced by toxic dose of acetaminophen to near normal after either rutin or NAC treatment while ALT levels did not. A similar observation has been reported by Yin et al. (1999) and Ronis et al. (2005) where ALT levels were poorly correlated with ethanol-induced liver injury in both human and rats.

On the other hand, the residual mild hydropic degeneration may explain the high ALT levels found at the end of therapy. Although acetaminophen induced significant elevation in ALT levels that are closely parallel to histopathological liver damage, yet, some other toxins have been reported to increase serum ALT with no histopathological liver finding (Wang et al., 2011).

It is well known that excessive APAP in hepatocytes is metabolized into NAPQI mainly by number of isozymes of cytochrome P450. Accumulated NAPQI kills hepatocytes by depletion of GSH accompanied by oxidative stress (Jaeschke et al., 2002).

NAPQI reacts with GSH, leading to its depletion by as much as 90%. Subsequently, the metabolite covalently binds to he-

patic cellular proteins and the lipid bilayer of hepatocyte membranes. Paracetamol was found to cause statistically significant increase in malondialdehyde quantity both in vitro and in vivo (Simeonova et al., 2013) and may result in hepatocellular death and centrilobular liver necrosis (Ray et al., 1996; McConnachie et al., 2007).

The inhibitors of cytochrome P-450 (CYPs) are known to reduce the toxicity of paracetamol (Li et al., 1997), hence the reported inhibition of CYPs by rutin (Bear and Teel, 2000) might have contributed favorably toward its observed hepatoprotection (Chang et al., 1993).

Inflammation plays a central role during drug-induced acute hepatitis and leukotrienes, the 5-lipoxygenase products of arachidonic acid metabolism have been extensively involved in the inflammatory processes (Perez-Alvarez et al., 1993). The reported anti-inflammatory (Aleksandrov et al., 1986) and 5-lipoxygenase inhibitory (Swies et al., 1984) activities of rutin

may also be partly involved in the protective effect against acetaminophen induced hepatotoxicity observed in this study.

Interestingly, the use of multiple doses of rutin can decrease ALT levels induced by acetaminophen overdose rather than the single dose of NAC. N-acetyl cysteine is given to stimulate the production of GSH. In clinical practice, NAC is usually used in multiple doses but experimentally as a single dose. This may explain the lower efficacy of NAC in the present study.

In conclusion, the results of the present study prove that multiple doses of rutin are more efficient for improving acute hepatotoxic effects induced by acetaminophen than a single dose of NAC. If another future work show the same beneficial effects of rutin compared to multiple doses of NAC, we think that at least a rationale base exists to start checking if this effect seen in mice, is observable in human too.

**Figure (1):** Section in the liver from a control mouse showing normal hepatic architecture (Hx & E X 200).

**Figure (2):** Section in the liver from a control mouse showing minimal portal inflammation (Hx & E X 400).

**Figure (3):** Section in the liver from a mouse that was given rutin showing normal hepatic architecture (Hx & E X 400).

**Figure (4):** Section in the liver from a mouse that was given N acetyl cysteine showing normal hepatic architecture (Hx & E X 400).

**Figure (5):** Section in the liver from a mouse that was given acetaminophen showing portal inflammation (Hx & E X 400).

**Figure (6):** Section in the liver from a mouse that was given acetaminophen showing centrilobular necrosis and apoptosis (Hx & E X 400).

**Figure (7):** Section in the liver from a mouse that was given acetaminophen showing centrilobular hydropic degeneration (Hx & E X 200).

**Figure (8):** Section in the liver from a mouse that was given acetaminophen showing macro and micro-vesicular steatosis (Hx & E X 400).

**Figure (9):** Section in the liver from a mouse that was given acetaminophen followed by rutin showing mild portal inflammation and hydropic degeneration (Hx & E X 400).

**Figure (10):** Section in the liver from a mouse that was given acetaminophen followed by N acetyl cysteine showing mild portal inflammation (Hx & E X400).



**Table (1)** : Comparison between control and different test groups regarding ALT levels (n=60)

	Negative control n (10)	Acetaminophen n (10)	Rutin n (10)	NAC n (10)	APAP treated by Rutin, n (10)	APAP treated by NAC, n (10)
Mean $\pm$ SD	112.10 $\pm$ 42.22	292.40 $\pm$ 119.20	75.10 $\pm$ 6.35	78.70 $\pm$ 6.29	163.70 $\pm$ 25.37	215.80 $\pm$ 27.17
Median (range)		340.5 (115 – 405)	73.5 (65 – 84)	78 (70 – 91)	164 (106 – 200)	212.50 (190 – 284)
P		0.001*	0.022*	0.034*	0.004*	0.000*
P1					0.008*	0.076
P2						0.000*

APAP: acetaminophen, NAC: N acetyl cysteine, P: is for comparison with negative control group, P1: is for comparison with acetaminophen group, P2: is for comparison between groups treated with NAC and that treated with rutin following acetaminophen acute toxicity,  $P < 0.05$  is considered significant.

**Table (2) :** Cross tabulation of histopathological results of the mice liver in the tested groups (n= 60)

Groups (Each is 10 mice)	Zone I								Zone III							
	Hydropic degeneration				Inflammatory reactions				Inflammatory reactions				Apoptosis			
	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Normal n (%)	Mild N (%)	Moderate n (%)	Severe n (%)	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Control	10 (100)	0	0	0	4 (40)	6 (60)	0	0	10 (100)	0	0	0	10 (100)	0	0	0
Acetaminophen	7 (70)	0	3 (30)	0	6 (60)	1 (10)	3 (30)	0	0	3 (30)	6 (60)	1 (10)	2 (20)	0	8 (80)	0
Rutin	10 (100)	0	0	0	10 (100)	0	0	0	10 (100)	0	0	0	10 (100)	0	0	0
NAC	10 (100)	0	0	0	10 (100)	0	0	0	10 (100)	0	0	0	10 (100)	0	0	0
APAP treated by Rutin	5 (50)	5 (50)	0	0	9 (90)	1 (10)	0	0	10 (100)	0	0	0	10 (100)	0	0	0
APAP treated by NAC	7 (70)	3 (30)	0	0	7 (70)	3 (30)	0	0	10 (100)	0	0	0	10 (100)	0	0	0

APAP: acetaminophen, NAC: N acetyl cysteine,

**Table (3) :** Histopathological results of the mice liver in the tested groups (n=60)

Groups (Each is 10 mice)	Zone I				Zone III			
	Hydropic degeneration		Inflammatory reactions		Inflammatory reactions		Apoptosis	
	Normal n (%)	Mild n (%)	Normal n (%)	Mild n (%)	Normal n (%)	Moderate n (%)	Normal n (%)	Moderate n (%)
<b>Control</b>	10 (100)	0	4 (40)	6 (60)	10 (100)	0	10 (100)	0
<b>Acetaminophen</b>	7 (70)	0	6 (60)	1 (10) P = 0.133	0	6 (60) P = 0.0001*	2 (20)	8 (80) P = 0.0007*
<b>Rutin</b>	10 (100)	0	10 (100)	0 P = 0.005	10 (100)	0 P1 = 0.0001*	10 (100)	0 P1 = 0.0007*
<b>NAC</b>	10 (100)	0	10 (100)	0 P = 0.005	10 (100)	0 P1 = 0.0001*	10 (100)	0 P1 = 0.0007*
<b>APAP treated by Rutin</b>	5 (50)	5 (50) P = 0.032* P1=0.044*	9 (90)	1 (10) P = 0.057 P1= 1.00	10 (100)	0 P1 = 0.0001*	10 (100)	0 P1 = 0.0007*
<b>APAP treated by NAC</b>	7 (70)	3 (30) P = 0.21 P1=0.23 P2 = 0.65	7 (70)	3 (30) P = 0.37 P1 = 0.60 P2 = 0.58	10 (100)	0 P1 = 0.0001*	10 (100)	0 P1 = 0.0007*

APAP: acetaminophen, NAC: N acetyl cysteine, P: is for comparison with negative control group, P1: is for comparison with acetaminophen group, P2: is for comparison between groups treated with NAC and that treated with rutin following acetaminophen acute toxicity, P < 0.05 is considered significant.

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## هل يمكن استخدام الروتن كترياق لعلاج التأثير السمي على الكبد نتيجة التسمم الحاد بالأسيتامينوفين؟ دراسة تجريبية

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كلية الطب - جامعة المنصورة

يعتبر الأسيتامينوفين من أكثر العقاقير استخداما في العالم، ولا تزال الإصابة الحادة للكبد الناجمة عن جرعة زائدة من الأسيتامينوفين تمثل مشكلة سريرية هامة. الهدف من هذه الدراسة هو تقييم استخدام الروتن كترياق في علاج التسمم الحاد بالاسيتامينوفين مقارنة مع العلاج المعتاد بواسطة N-أسيتيل سيستين في الفئران. وقد شملت هذه الدراسة ستين فأرا تم تقسيمهم إلى ٦ مجموعات متساوية على النحو التالي: المجموعة الاولى: مجموعة ضابطة، المجموعة الثانية: تم إعطاؤها جرعة سامة من الاسيتامينوفين (٢٥٠ مجم / كجم حقنا في الغشاء البريتوني). المجموعة الثالثة: تم إعطاؤها N أسيتيل سيستين (٢٠٤ مجم / كجم حقنا في الغشاء البريتوني). المجموعة الرابعة: تم إعطاؤها الروتن (٢٨ مجم / كجم عن طريق الفم). المجموعة الخامسة: تم إعطاؤها جرعة سامة من الاسيتامينوفين تليها جرعة من N-أسيتيل سيستين بعد ساعة واحدة عبر الغشاء البريتوني. والمجموعة السادسة: تم إعطاؤها جرعة سامة من الاسيتامينوفين يليها بعد ساعة واحدة أربع جرعات من الروتن عن طريق الفم (جرعة / ١٢ ساعة). وقد تم ذبح الفئران بعد ١٢ ساعة من الجرعة الاخيرة وتم تجميع عينات الدم من أجل تحديد مستوى انزيم ألانين ترانس أميناز ثم تشريح الفئران واستخراج الكبد وفحصه بالميكروسكوب العادي. وقد أظهرت هذه الدراسة أن الجرعات المتعددة من الروتن كانت أفضل في علاج التأثير السمي لجرعة زائدة من عقار الاسيتامينوفين على الكبد بدلا من جرعة واحدة من N-أسيتيل سيستين حيث تحسن مستوى انزيم ألانين ترانس أميناز و تحسنت التغيرات الهستوباثولوجية في الكبد. ويستنتج من ذلك أن الروتن يمكن استخدامه في علاج التأثير السمي على الكبد نتيجة التسمم الحاد بالأسيتامينوفين.