

Effect of N-acetylcysteine on Hepatic Ischemia-reperfusion Injury in Normal and Steatotic Rats

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ABSTRACT

Background: Liver ischemia-reperfusion (I/R) injury occurs during major liver surgery, transplantation or following haemorrhagic shock with subsequent fluid resuscitation. Liver steatosis is a risk factor in liver transplantation and liver resection. **Aim:** This study was undertaken to evaluate the effect of N-acetylcysteine (NAC) on hepatic I/R injury in both normal and steatotic rat livers. **Material and methods:** 48 male wistar rats, divided into 2 equal groups, steatosis was induced in one of them by high cholesterol diet for 8 weeks. Each of these 2 groups was subdivided into 3 subgroups; control, I/R, I/R+ NAC groups. At the end of experiment, liver enzymes, inflammatory, lipid peroxidation and oxidative parameters were assessed and histopathological examination of liver samples was done to prove the incidence of steatosis. **Results:** NAC produced significant reduction in liver enzymes, inflammatory, lipid peroxidation parameters and significant increase in antioxidant parameters in both normal and steatotic rats. **Conclusion:** NAC may be considered as a promising therapeutic candidate for chemoprevention of hepatic I/R injury through its antioxidant, anti-inflammatory, antifibrotic, antiapoptotic and antisteatotic effects in either normal or steatotic livers.

Keywords: Ischemia-reperfusion, N-acetylcysteine, steatosis.

INTRODUCTION

Liver ischemia-reperfusion (I/R) injury occurs during major liver surgery, transplantation or following hemorrhagic shock and subsequent fluid resuscitation⁽¹⁾. The pathophysiology of I/R injury involves the activation of many metabolic pathways and release of mediators that induce liver injury⁽²⁾.

There is growing evidence that there are two distinct phases of liver injury after warm I/R, the early phase (up to 2 hr post-reperfusion) is characterized by activation of kupffer cell-induced oxidative stress⁽³⁾. In the late phase (4-24 hr post-reperfusion),

the main event is accumulation of activated neutrophils and the production of free radicals and proteases⁽⁴⁾. One of the most important components of intracellular antioxidant system is glutathione (GSH), a powerful active radical scavenger that is depleted during severe liver I/R injury⁽⁵⁾. Exogenous GSH cannot enter the cell, so its intracellular buildup requires cysteine, which is its major constituent, to be supplied from outside. N-acetylcysteine (NAC) is an exogenous GSH precursor⁽⁶⁾.

In the last thirty years, hepatic steatosis has been well-documented as most common chronic liver disease in

general population⁽⁷⁾. Either as isolated or cooperative factors; mitochondrial dysfunction, inflammatory cytokines, free fatty acids, endotoxin, microvascular injury and oxidative stress may all be involved in the pathogenesis of ischemia-reperfusion injury⁽⁸⁾. In this study, we assessed the effect of NAC on hepatic I/R injury in both normal and steatotic rat livers.

MATERIAL & METHODS

Drugs:

1. N-acetylcysteine (Sigma Co., USA).
2. Cholesterol powder (Winlab Company for Pharmaceuticals).

Animal model for I/R:

Anaesthesia was induced by intramuscular injection of 0.5ml/kg body weight fentanyl-fluanisone. Rats then underwent inhalation anaesthesia with isoflurane (0.5-2%). Rectal temperature was maintained at 35-37°C with warming blanket. A median laparotomy was performed, the ligaments of the liver were cut, all structures in the portal triad (hepatic artery, portal vein and bile duct) of the median and left lobes of the liver were clamped by using a traumatic microvascular clip and the abdomen was closed. After one hour, a second labarotomy was performed and the clip was removed, and the animals were kept alive for 4hr after reperfusion.

Experimental groups and protocol:

Forty eight adult male wistar rats that weighed 200-250 gm were maintained in a daily 12 hr light-dark cycle, room temperature and free access to tap water. Steatosis was

induced by feeding the animal with a high cholesterol (2%) diet for 8 weeks⁽³⁾ in twenty four rats. The other twenty four rats were fed a standard balanced diet. Each group was furtherly subdivided into 3 subgroups, each of 8 rats as follow:

1. **Group IA (Control group):** Sham-operated without I/R and received vehicle (20ml of 5% dextrose over 30min then continued at rate of 10ml/h over 4 hours).
2. **Group IIA (I/R group):** I/R was performed and received vehicle (20ml of 5% dextrose over 30 min before reperfusion and continued at rate of 10ml/h over 4 hours reperfusion period).
3. **Group IIIA (NAC + I/R group):** I/R was performed and received NAC (150mg/kg body weight in 20 ml of 5% dextrose was infused intravenously through the tail vein over 30 min before reperfusion and maintained at 10 ml/kg/hr in 5% dextrose during the 4 h reperfusion period⁽⁴⁾.
4. **Group IB (Steatotic control):** Sham-operated without I/R and received vehicle as in group IA.
5. **Group IIB (Steatotic I/R):** I/R was performed and received vehicle as in group IIA.
6. **Group IIIB (NAC + steatotic I/R):** I/R was performed and received NAC in the same dose as group IIIA.

At the end of the experiment, arterial blood samples were collected into EDTA-coated tubes and serum was separated and stored until analysis. Liver was quickly excised for analysis and histopathology. Then animals were killed by exanguination.

Methods:

Determination of serum alanine aminotransferase (ALT)⁽⁹⁾, alkaline phosphatase (AP)⁽¹⁰⁾ and lactate dehydrogenase LDH⁽¹¹⁾ by enzymatic colorimetric methods, and are expressed as U/L.

Tumour necrosis factor- α (TNF- α) was estimated by Commercial Sandwich ELISA kits for rats according to manufacturer's instructions (Biosource, International, Camarillo, California, USA)⁽¹²⁾, and expressed as Pg/ml.

Malondialdehyde (MDA) was measured by thiobarbituric acid method ⁽¹³⁾ and is expressed as $\mu\text{mol/ml}$.

Reduced glutathione (GSH) by fluorometric method of Hissin and Hifi ⁽¹⁴⁾, and is expressed as nmol/mg protein.

Measurement of Catalase ⁽¹⁵⁾ by peroxide substrate method and is expressed as U/gm tissue.

Histopathological examination:

Sections of liver were taken, kept in formalin and fixed in paraffin blocks. Then cut by microtome and stained by hematoxylin and eosin to prove the incidence of steatosis.

Statistical analysis:

Data were expressed as mean + SD. Statistical difference involving multiple group comparisons were determined by one way ANOVA, followed by scheffe (F) test. The least significant different mean values ($P < 0.05$) was accepted to denote significant difference. This is done by

using SPSS computer program version 16.

RESULTS

As shown in table (1,2) and Fig. (1, 2, 3, 4, 5 and 6) :

Steatosis produced significant increase in TNF- α and MDA and significant reduction in reduced GSH ($P < 0.05$) when compared to the normal control group. Steatosis and inflammatory infiltration were also evident by histopathological examination (Fig.5,6).

I/R either in normal control or steatotic rats produced significant increase in liver enzymes (ALT, AP and LDH), TNF- α and MDA ($P < 0.05$) and significant reduction in reduced GSH and catalase ($P < 0.05$) when compared to either control or steatotic groups respectively.

I/R in steatotic group also produced significant increase in liver enzymes (ALT, AP and LDH) and MDA ($P < 0.05$) when compared to I/R in normal rats.

NAC administration during I/R either in normal or steatotic rats produced significant reduction in liver enzymes (ALT, AP and LDH), TNF- α and MDA ($P < 0.05$) and significant increase in reduced GSH and catalase enzyme ($P < 0.05$) when compared to I/R in either normal or steatotic groups respectively.

Table (1): Mean and standard deviation of liver enzymes among studied groups.

Group Parameter	Control	I/R	NAC +I/R	Steatosis	Steatosis +I/R	Steatosis +I/R +NAC	F	Relations
	IA	IIA	IIIA	IB	IIB	IIIB		
ALT u/l	26.35 +5.51	125.71 +20	48.42 +4.43	29.86 +5.59	172.49 +22.92	70.66 +11.97	142.85	IIA vs IA* IIB vs IB*
AP u/l	51.49 +8.91	97.48 +11.94	62.86 +10.66	57.589 +11.42	210.86 +24.86	96.06 +12.01	138.75	IIB vs IIA* IIIA vs IIA*
LDH u/l	61.61 +13.99	94.60 +13.13	71.46 +10.51	65.70 +12.83	150.85 +15.19	100.99 +14.49	12.01	IIIB vs IIB*

* Significant (P<0.05).

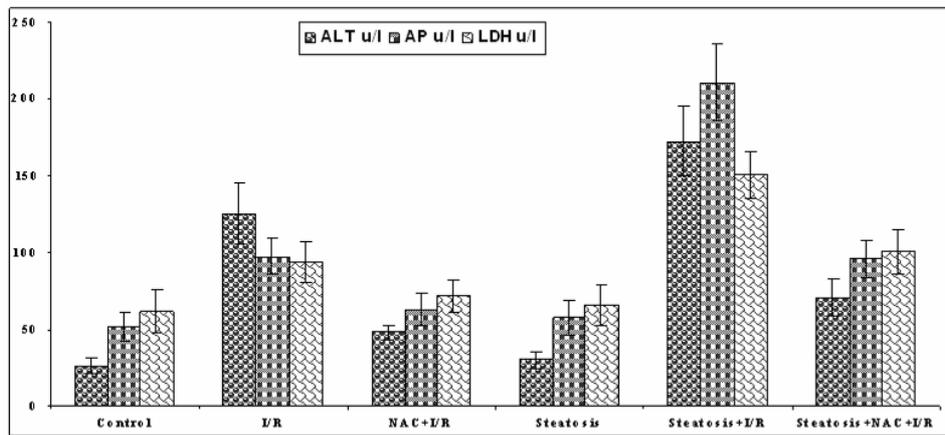


Fig. (1): Mean and standard deviation of liver enzymes among studied groups

Table (2): Mean and standard deviation of TNF- α , MDA, reduced GSH and catalase among studied groups.

Group Parameter	Control	I/R	NAC +I/R	Steatosis	Steatosis +I/R	Steatosis +I/R +NAC	F	Relations
	IA	IIA	IIIA	IB	IIB	IIIB		
TNF- α pg/ml	33.58 \pm 8.96	90.73 \pm 8.37	60.36 \pm 8.13	54.59 \pm 8.96	101.85 \pm 10.48	101.85 \pm 10.78	56.80	IA vs IB* except in catalase IIA vs IA* IIB vs IB* IIB vs IIA* only in MDA IIIA vs IIA* IIIB vs IIB*
MDA umol/ml	1.32 \pm 0.16	1.91 \pm 0.09	1.28 \pm 0.14	1.62 \pm 0.27	2.24 \pm 0.21	1.57 \pm 0.15	34.21	
reduced GSH nmol/mg	8.70 \pm 0.57	6.71 \pm 0.51	8.88 \pm 0.75	7.71 \pm 0.60	6.54 \pm 0.43	7.72 \pm 0.43	23.98	
Catalase u/gm	188.96 \pm 8.88	164.71 \pm 7.70	201.23 \pm 14.06	177.66 \pm 8.77	157.73 \pm 10.88	187.61 \pm 12.66	18.37	

* Significant (P<0.05).

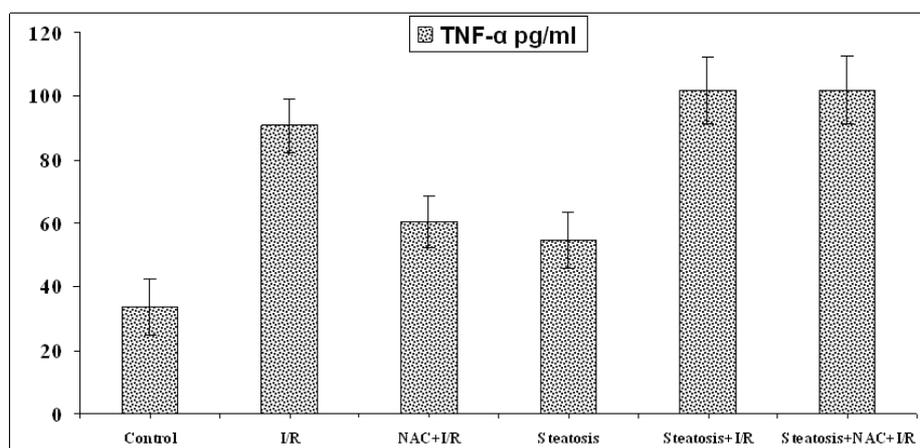


Fig. (2): Mean and standard deviation of TNF- α among studied groups

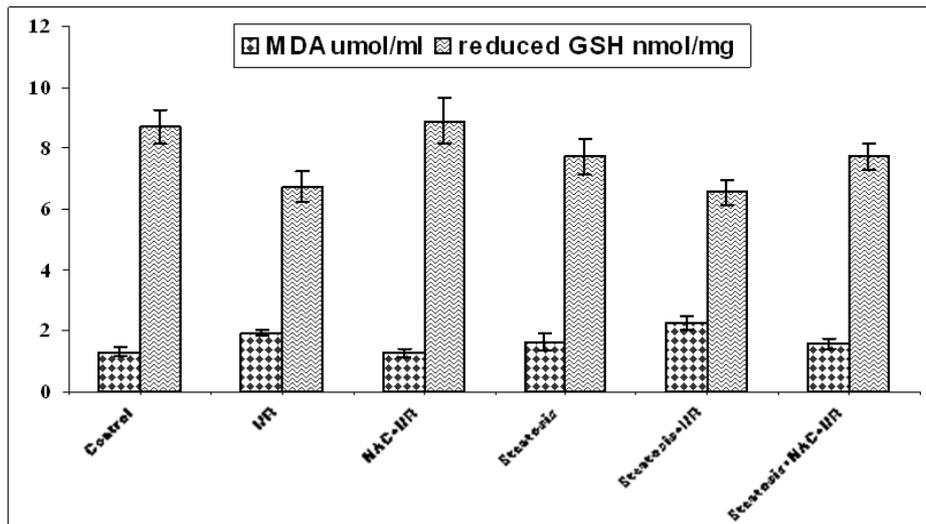


Fig. (3): Mean and standard deviation of MDA, reduced GSH among studied groups

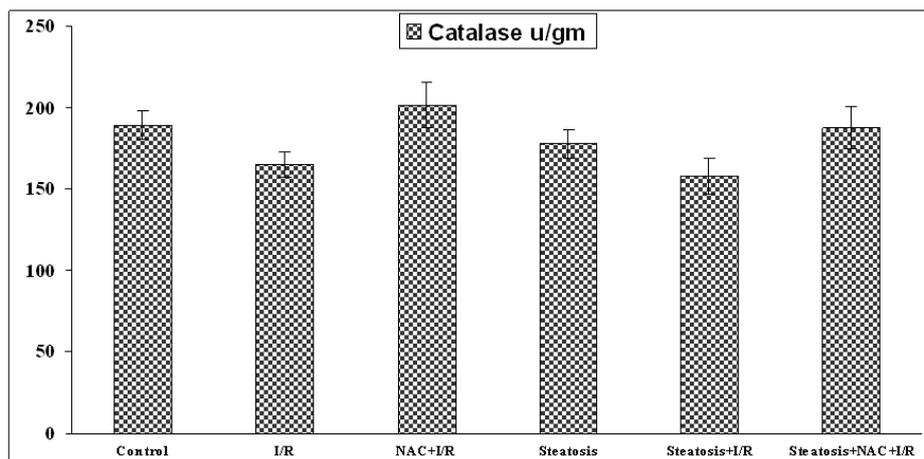


Fig. (4): Mean and standard deviation of Catalase among studied groups

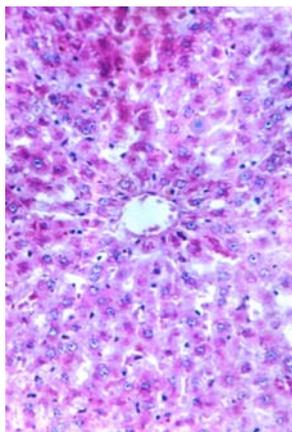


Fig. (5): Section in liver showing normal liver architecter. (H x & E x 400)

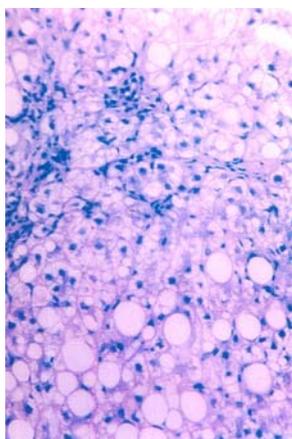


Fig. (6): Section in liver received high cholesterol diet showing extensive steatosis (++++) with moderate inflammatory infiltration (+++). (H x & E x 400)

DISCUSSION

The induction of hepatic steatosis in this study was accompanied by inflammation, lipid peroxidation and decreased level of intracellular free radical scavenger. This confirms the

vulnerability and increased susceptibility of the steatotic livers to I/R injury. So, hepatic inflammation and oxidative stress are already present in steatotic livers and aggravated in ischemic liver injury during reperfusion. These results are agreed by many authors^(16,17).

Mitochondria are involved in fatty acid β oxidation and oxidative phosphorylation. Additionally, these organelles are an important source of reactive oxygen species (ROS) and impairment of their activity plays a central role in steatotic liver damage⁽¹⁶⁾. Mitochondrial-oxidation impairment leading to increased free fatty acids inside hepatocytes which increases the cell volume resulting in decreased sinusoidal space and impaired microcirculatory blood flow up to 50% in fatty liver⁽¹⁸⁾. At the same time, the free fatty acids inhibit acetyl coenzyme A, an important cofactor in krebs cycle and gluconeogenesis, thus leading to decreased production of adenosine triphosphate (ATP)⁽¹⁹⁾.

It is clear from our results that I/R produced significant increase in inflammatory marker (TNF- α) and oxidative stress (increased MDA and decreased reduced GSH and catalase) in both normal and steatotic rats in comparison to their control groups and still significant increase in steatotic I/R when compared to I/R in normal rats.

I/R causes mitochondrial dysfunction and increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) leading to generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Both can cause cellular injury

through peroxidation of membrane lipids, protein denaturation and oxidative DNA damage⁽²⁰⁾.

Reactive nitrogen species (RNS) like peroxynitrite is a highly reactive free radical formed by combination of nitric oxide (NO) with superoxide anions. Under normal conditions, this reaction is prevented by continuous removal of NO by haemoglobin. Nonetheless, during later stage of reperfusion, NO production increases as a result of the expression of inducible nitric oxide synthase (iNOS). Excessive NO production leads to formation of peroxynitrite which causes mitochondrial dysfunction, impaired circulation and hepatic injury⁽²¹⁾.

Nuclear factor kappa B (NF-kappa B) is activated by oxidative stress during hepatic I/R and may play a significant role in the induction of inducible nitric oxide synthase (iNOS) gene⁽²²⁾. The humoral induction of inflammatory mediators such as cytokines and eicosanoids may also be involved⁽²¹⁾.

The sinusoidal microcirculatory impairment during reperfusion has been also implicated in the pathogenesis of liver damage and may be caused by sinusoidal vasoconstriction mediated by an altered endothelin-NO balance⁽²³⁾, sinusoidal endothelial cell swelling with luminal narrowing⁽²⁴⁾ and/or increased expression of adhesion molecules with subsequent leukocyte and endothelial cell interaction⁽²⁵⁾.

Activation of toll-like receptor 2 and 4 gene may play an important role in the ROS-induced liver injury after I/R. Signaling by toll-like receptors occurs through activation of NF-kappa

B and JNK/SAPK which is activated by ROS. ROS can also modify membrane components and is a known inducer of apoptosis and necrosis⁽⁶⁾.

NAC succeeded to significantly reduce liver enzymes (ALT, AP and LDH), inflammation (TNF- α) and lipid peroxidation (MDA) and also to significantly increase reduced GSH and catalase when administered during I/R either in normal or steatotic rats.

NAC is a thiol-containing compound that directly interacts and detoxifies free radicals by non enzymatic reactions (free radical scavenger)⁽²⁶⁾. It is also deacetylated to form cysteine which is the precursor of glutathione, one of the most important components of intracellular antioxidant system⁽²⁷⁾. By its antioxidant action, it inhibits lipid peroxidation, it also potentiates γ -aminolevulinic acid dehydratase activity, an effect that is not related to hepatic peroxidation⁽²⁸⁾.

The anti-inflammatory effect of NAC may be related not only to inhibited expression of (iNOS), but it also blocks the upregulated NF-kappa B binding activity after liver reperfusion⁽²²⁾. NAC also inhibits expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 (ICAM-1 and VCAM-1) and causes shedding of selectins which might be contributing factors to decrease leukocyte adherence and improve microcirculatory haemodynamics⁽²⁹⁾. It was also proven that NAC inhibits activation of toll-like receptor 2 and 4 mRNA and protein and the induction of TNF- α resulting from I/R injury via

modulating redox state. Thus, it may mitigate liver injury following I/R in mice⁽⁵⁾.

NAC seems to attenuate hepatic I/R injury through decreasing platelet activation, increasing cAMP in ischemic liver tissue, and decreasing the activity of glutathione-S-transferase⁽³⁰⁾.

The antifibrotic role was also stated via inhibition of stellate cell activation⁽³¹⁾ and inhibition of profibrotic cytokine, liver transforming growth factor-beta (TGF-beta)⁽³²⁾.

Many authors proved the antiapoptotic effect of NAC through inhibiting the cell cycle arrest at the S and G2/M phase and shifting the cells to G1 phase thus decreasing the degree of DNA damage and increasing the cell viability^(33,34).

The antisteatotic effect of NAC has been suggested through two mechanisms. First, that NAC replenishes the mitochondrial GSH pool and restores the mitochondrial function and enhances regeneration of ATP, thus leading to reduced ROS generation⁽³⁵⁾. Second, that NAC may minimize damage to circulation in liver, thus reducing haemorrhage in ischemic livers⁽⁴⁾.

CONCLUSION

NAC prevents liver tissue damage and may be considered as a promising therapeutic candidate for chemoprevention of I/R injury through antioxidant, anti-inflammatory, antifibrotic, antiapoptotic and antisteatotic effects either in normal or steatotic livers. Thus, it may have a role in increasing the cell

viability, preventing the early graft rejection and increasing survival rate during liver surgery and transplantation.

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الملخص العربي

الهدف من البحث: هو معرفة تأثير ن-أسيتيل سيستئين على الضرر الكبدى الناتج عن نقص التدفق الدموى الموضعى ثم إعادة الإشباع الدموى فى الفئران الطبيعية والمصابة بالكبد الدهنى المستحدث بالكوليسترول. **طريقة البحث:** أجرى هذا البحث على ٤٨ من الفئران الذكور قسمت إلى مجموعتان متساويتان أ ، ب . تم إحداث إصابة بالكبد الدهنى بالكوليسترول فى مجموعة ب . ثم تم تقسيم كل مجموعة إلى ثلاث مجموعات متساوية كل منها (٨ فئران) كما يلى:

١. **المجموعة الأولى أ:** مجموعة ضابطة طبيعية.
٢. **المجموعة الثانية أ:** تم إحداث نقص تدفق الدم الموضعى ثم إعادة الإشباع الدموى لمدة ٤ ساعات.
٣. **المجموعة الثالثة أ:** تناولت عقار ن – أسيتيل سيستئين أثناء إجراء نقص تدفق الدم الموضعى ثم إعادة الإشباع الدموى لمدة ٤ ساعات.
٤. **المجموعة الأولى ب:** مجموعة الكبد الدهنى (ضابطة).
٥. **المجموعة الثانية ب:** تم إحداث نقص التدفق الدموى الموضعى ثم إعادة الإشباع الدموى لمدة ٤ ساعات.
٦. **المجموعة الثالثة ب:** تناولت عقار ن-أسيتيل سيستئين أثناء إجراء نقص التدفق الموضعى ثم إعادة الإشباع الدموى لمدة ٤ ساعات.

فى نهاية التجربة تم جمع عينات الدم وعينات من الكبد لقياس:

١. إنزيمات الكبد (الأنين ترانسفيراز ، كرياتين فوسفات واللاكتات ديهيدروجيناز).
٢. عامل تنخرز الأورام ألفا.
٣. المالونديالدهيد.
٤. الجلوتاثيون المختزل.
٥. أنزيم الكتالاز.

كما تم عمل دراسة هستوباثولوجية لاثبات حدوث الكبد الدهنى.

النتائج:

١. تم إحداث الكبد الدهنى بالكوليسترول.
 ٢. نقص تدفق الدم الموضعى ثم الإشباع الدموى أحدث ضرراً بالغاً بالكبد سواء فى الفئران الطبيعية أو المصابة بالكبد الدهنى.
 ٣. عقار ن أسيتيل سيستئين أحدث نقص ذو دلالة احصائية فى إنزيمات الكبد ، عامل تنخرز الأورام ألفا والمالونديالدهيد وأيضاً أحدث زيادة ذات دلالة احصائية فى الجلوتاثيون المختزل وإنزيم الكتالاز بالمقارنة بمجموعات نقص التدفق الدموى ثم الإشباع الدموى فى الفئران الطبيعية والمصابة بالكبد الدهنى.
- الاستنتاج:** أظهرت نتائج البحث أن لعقار ن – أسيتيل سيستئين تأثير وقائى ضد الأذى الناتج عن نقص التدفق الدموى ثم الإشباع الدموى فى الفئران الطبيعية والمصابة بالكبد الدهنى.