Research Article

Evaluation the anti-inflammatory effect of Omega 369 against acetaminophen-induced hepatotoxicity in mice

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Abstract

Background: Acetaminophen (N-acetyl-para-aminophenol, or APAP) poisoning, whether intentional or accidental, is a major general health problem, with its toxicity prevalence significantly increasing in many countries. Currently, acetaminophen is considered one of the main causes of acute liver failure globally.

Aim: The aim of this study was to evaluate the possible hepatoprotective effect of Omega-3,6,9 against acetaminophen-induced hepatotoxicity in albino male mice.

Methods: Thirty-five albino male mice were randomly divided into five groups: Group 1 (the negative control) received liquid paraffin orally at a dose of 10 ml/kg for ten days, followed by a single intraperitoneal injection (IP) of 10 ml/kg normal saline on the eleventh day of the test. Group 2 (positive control) received liquid paraffin. Group 3 was treated with Omega-3,6,9 (50 mg/kg/80 mL). Group 4 was treated with Omega-3,6,9 (100 mg/kg/35 mL). Group 5 was treated with N-acetylcysteine (100 mg/kg/10 ml). The mice were treated with Omega-3,6,9, N-acetylcysteine, and liquid paraffin once daily by oral gavage for ten days.

Result: TNF-α, IL-10, ALT, and AST levels in the positive control group were significantly higher than those in the negative control group. TNF-α, IL-10, ALT, and AST levels in mice given Omega-3,6,9 (50 mg/kg), Omega-3,6,9 (100 mg/kg), and N-acetylcysteine (100 mg/kg) orally prior to acetaminophen injection were significantly decreased compared to those in the positive control group.

Conclusion: Oral intake of Omega-3,6,9 may reduce the risk of acetaminophen-induced liver damage.

Keywords

Introduction

The liver is the most critical organ responsible for the metabolism and detoxification of several medications; however, it can also be affected by several side effects or medication toxicity that can cause liver damage. Although some medications have little to no metabolism within the liver, most pharmaceuticals undergo some liver metabolism before being excreted by the kidneys or bile (Al-Rikabi and Alshawi 2016). Drug-induced hepatotoxicity is a severe condition, now the primary factor in hepatic dysfunction

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and accounting for 20–40% of liver transplant cases in the US. These medications use different mechanisms, including oxidative stress, fatty acid peroxidation, fat buildup, antibody-mediated cytotoxicity, and apoptosis, to damage liver cells (Mahmood and Askar 2022).

Acetaminophen, also known as N-acetyl-para-aminophenol (APAP), is one of the most frequently utilized medications and is relatively safe compared to other non-steroidal anti-inflammatory drugs. However, an APAP overdose can cause various liver problems, including increased liver enzymes, abrupt liver failure, and hepatic encephalopathy (Hameed and Hassan 2022). At the therapeutic level, the primary metabolic pathways of APAP involve conjugation with glucuronic acid and sulfate, which are then excreted in the urine (McGill andJaeschke 2013). However, a tiny amount of APAP can be oxidized by cytochrome P450 (CYP450) activity to form the potentially reactive molecule N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is largely processed by CYP2E1 and subsequently combined with hepatic glutathione before being eliminated in the urine (Zaher et al. 1998; Ramachandran and Jaeschke 2017).

Large doses of APAP can lead to glutathione depletion due to increased NAPQI synthesis and saturation of its main metabolic pathways (glucuronidation and sulfation) (Zaher et al. 1998; Ghanem 2016). NAPQI is then attached to macromolecules in the liver, leading to irreversible hepatic necrosis (Hamad 2016; Al-Kuraishy 2019). Severity of liver injury is indicated by changes in multiple hepatic indicators, such as serum alanine aminotransferase (SALT), serum aspartate aminotransferase (SAST), and serum alkaline phosphatase (SALP) (Al-Razzuqi 2012). Liver damage results in a severe inflammatory process characterized by an increase in cell inflow and production and release of inflammatory mediators, primarily tumor necrosis factor-alpha (TNF-alpha) (Martin-Murphy 2010; Kim et al. 2013). TNF-alpha is a crucial regulator that affects inflammation in various ways by causing the release of other cytokines and chemokines. N-acetylcysteine (NAC) is utilized as a therapy for APAP toxicity to avoid cell damage from NAPQI and enhance clinical outcomes (Smilkstein 1988).

Omega-3 fatty acids are utilized by the human body to make anti-inflammatory molecules called prostaglandins, which help the body maintain balance, particularly in the digestive system. These acids are essential for maintaining proper joint and brain function. Although omega-3s are generally beneficial, they can cause side effects when used in large quantities. Doctors recommend increasing omega-3 intake from fish or fish oil supplements to treat inflammatory conditions such as arthritis and chronic pain. However, some believe the risks of taking too much fish oil outweigh the benefits. This leads to the question of whether fish oil is a safe and effective way to manage inflammation (Al-hussainy 2022).

Omega-3 fatty acids are known to be beneficial in repairing damage caused by free radicals – harmful molecules that can damage cell structures. These radicals are naturally produced by the body during normal metabolic processes and are also introduced through environmental factors such as pollution and sun exposure. They lead to inflammation as the body tries to fight off the damage caused by them. Studies have shown that fish oil can reduce free radical damage in the body by up to 50 percent. This effect makes fish oil an important component of anti-aging products as it helps preserve youthful skin and prevent wrinkles and sagging.

Apart from reducing free radical damage, omega-3s inhibit COX-1 and COX-2 enzymes in certain bodily processes. COX-1 enzymes produce inflammatory prostaglandins in response to bodily trauma or damage, while COX-2 enzymes produce protective prostaglandins during normal metabolic processes. Though both COX enzymes are essential for bodily function, excessive COX activity leads to excess inflammation. Fish oil helps regulate these enzymes and reduce unwanted inflammation, thereby protecting cells and tissues from damage caused by free radicals or bodily trauma.

Another way omega-3s decrease inflammation is by protecting the liver from damage and reducing liver damage caused by drug toxicity (Al-hussainy 2022).

Drug toxicity occurs when a person takes too much of a particular drug or combines drugs that negatively interact with each other. Doctors may recommend increasing omega-3 intake from fish or fish oil supplements to treat inflammatory conditions such as arthritis and chronic pain (Aljuboury and Al-Shawi 2022). However, some believe this method is ineffective at reducing liver damage caused by drug toxicity or bodily trauma.

The body requires dietary lipids because they are critical to all biological systems. Except for long-chain fatty acids (FAs), which are classified into the Omega-3, Omega-6, and Omega-9 categories, all lipids may be synthesized by humans (Alexander 1998; Alhusseiny and El-Beshbishi 2020). When the body has adequate Omega-3 and Omega-6, it can create oleic acid (OA), a non-essential FA that belongs to the Omega-9 family (Elbossaty 2018).

Omega-3 fatty acids can stimulate or suppress the creation of pro- and/or anti-inflammatory cell signaling molecules and have been reported as agents that modulate inflammation. In a recent randomized controlled experiment, Omega-3 polyunsaturated fatty acid supplementation decreased blood proinflammatory cytokines (Johnson and Bradford 2014). Cod liver oil (CLO) contains omega-3 fatty acids and is crucial for maintaining normal health. Numerous studies have verified several beneficial effects of dietary n-3 PUFA, such as immunological response, lipid peroxidation, and antioxidative characteristics. Omega-3 PUFAs have been shown to have anti-inflammatory effects (Abdulwahid et al. 2016).

Methods

A total of thirty-five albino male mice, weighing 25–33 g, were used in this study. They were obtained and housed in the Animal House at the College of Pharmacy, University of Baghdad, under standardized conditions of temperature, humidity, and light/dark cycles. The mice were provided with regular pellet food and unlimited access to tap water. The experimental protocol was reviewed and approved by the scientific and ethical committee of the College of Pharmacy, University of Baghdad.

Acetaminophen (APAP) and Omega 369

Paracetamol ampoule of 500 mg/5 mL was purchased from Ajanta Pharma Limited (India) and Omega 369 was purchased from Adrien Gagnon, Canada.

Experimental design

Thirty-five albino male mice were divided randomly and equally into five groups and received their treatment as follows:

- **Group 1** – (Negative control) received liquid paraffin 10 ml/kg by oral gavage for 10 successive days, followed by a single intraperitoneal injection (IP) 10ml/kg normal saline on day 11 of the experiment.
- **Group 2** – (Positive control) received liquid paraffin 10 ml/kg by oral gavage for 10 successive days, followed by a single intraperitoneal injection (IP) of 400 mg/kg/10ml APAP on day 11 of the experiment (Nikravesh et al. 2018).
- **Group 3** – Treated with Omega 369 (50 mg/kg/80ml) by oral gavage for 10 successive days, followed by a single intraperitoneal injection (IP) of 400 mg/kg/10ml APAP on day 11 of the experiment.
- **Group 4** – Treated with Omega 369 (100 mg/kg/35 ml) by oral gavage for 10 days, followed by a single intraperitoneal injection (IP) of 400 mg/kg/10ml APAP on day 11 of the experiment.
- **Group 5** – Treated with NAC (100 mg/kg/10 ml) by oral gavage for 10 days, followed by a single intraperitoneal injection (IP) of 400 mg/kg/10ml APAP on day 11 of the experiment (Nikravesh et al. 2018).

Blood samples were obtained, serum was made, and mice's blood serum was tested for the level of alanine aminotransferase (ALT) ,aspartate aminotransferases (AST), tumor necrosis factor alpha (TNF-alpha) and interleukin 10 (IL10) after the animals in each group had been receiving therapy for 24 hours (Nikravesh et al. 2018). An enzyme-linked immunosorbent assay (ELISA) was used to measure TNF-α and IL10 level according to the instructions given on the kit by the manufacturer (MyBiosource, Inc, USA). The colorimetric method was used to measure concentration of (ALT) and (AST) according to the instructions given on the kit by the manufacturer (LINEAR CHEMICALS, SPAIN).

Statistical analysis

The investigation results are shown as mean and standard deviation (SD). The statistical analysis used the Statistical Package for the Social Sciences, version 25. (SPSS). An unpaired t-test was used to gauge the statistical significance between groups. At P< 0.05, statistics were deemed significant.

Results

The liver was shown in this investigation to be adversely affected by (APAP), but Omega 369 was shown to coun-
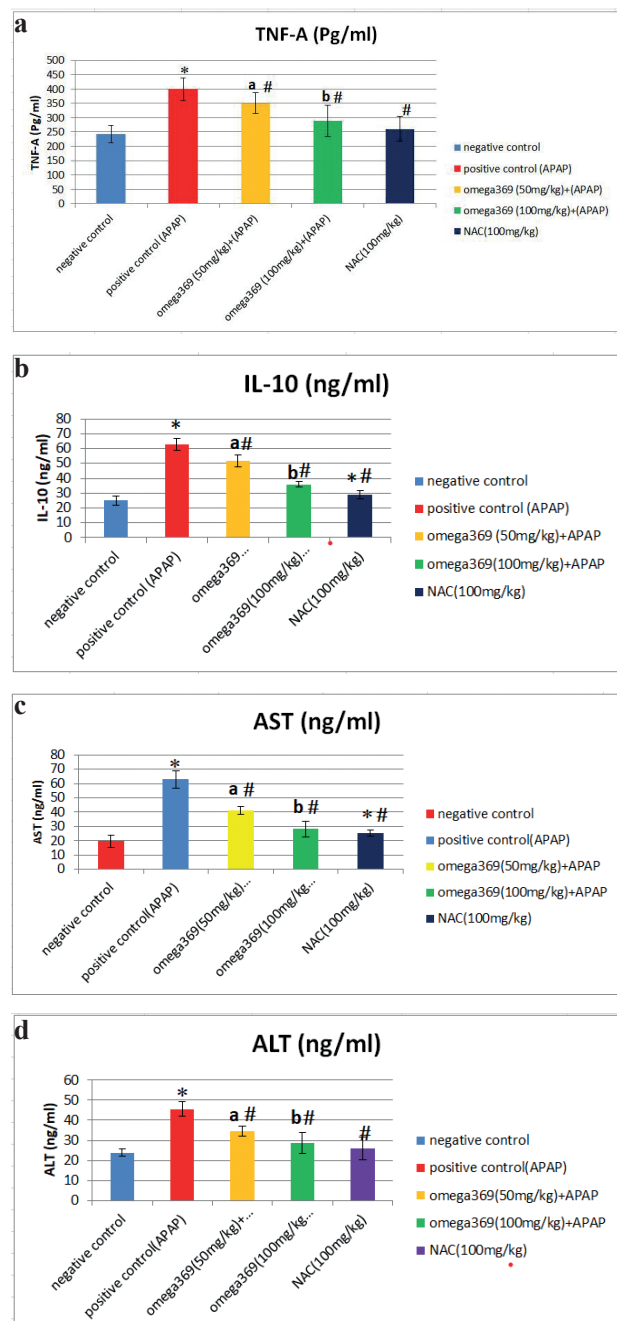

Figure 1. Effect of APAP, Omega 369, and NAC on (**a**) tumor necrosis factor-alpha (TNF-α) pg/ml (**b**) Interleukin 10 (IL-10) ng/ml (**c**) aspartate aminotransferase (AST) ng/ml (**d**) alanine aminotransferase (ALT) ng/ml. Values are mean±SD, n = 7; when compared to the negative control group, the use of superscript (*) reveals a significant variation (P<0.05). The superscript (#) denotes a significant difference (P< 0.05) compared to the Positive Control group. The difference between groups 3 and 4 is shown in superscripts (**a, b**) as being statistically significant (P < 0.05).

teract that effect. Fig. 1 reveals that TNF-α, IL10, AST, and ALT levels in the positive control group were significantly increased (P < 0.05) compared to those in the negative control group. Omega 369 at a dose (50 mg/kg), Omega 369 at a dose (100 mg/kg), and NAC (100 mg/kg) as a prophylactic treatment produced significant reduction (P < 0.05) in TNF-α, IL-10, AST and ALT levels as compared to those

in the positive control group. Furthermore, TNF-α, IL-10, AST, and ALT levels in mice given Omega 369 (50 mg/kg) and Omega 369 (100 mg/kg) were significantly different ($P < 0.05$) when comparing them. At the same time, a nonsignificant difference ($p > 0.05$) was observed in mice given NAC (100 mg/kg) when comparing TNF-α and ALT levels with those in negative control group.

Discussion

(APAP) overdose is a significant contributor to self-poisoning due to its easy accessibility and availability. According to reports, (APAP) is the drug that people intentionally or unintentionally overdose on the most across many nations (Gunnell et al. 1997; Taima 2023). An earlier study showed that oxidative stress is related to the development of (APAP) toxicity through the formation of the reactive compound NAPQI, resulting in peroxidation of lipids, antioxidant attenuation, mitochondrial dysfunction, and ultimately DNA damage and cell death by necrosis (Mohamed Kamel et al. 2022).

The current study discovered that mice in the positive control group had significantly higher TNF-α levels than those in the negative control group, indicating a severe inflammatory response. This finding is consistent with earlier studies that showed liver damage caused by (APAP) was associated with a significant rise in serum TNF-α levels (Fu et al. 2018; Bian et al. 2019). Hepatocyte necrosis brought on by (APAP)-induced oxidative stress triggers the influx of inflammatory cells and the inflammatory response (Du et al. 2016). Damage-associated molecular patterns (DAMPs) produced by necrosis in hepatocytes are detected by TLR4 and TLR9 (Mihm 2018), activating the innate immune system and releasing excessive amounts of inflammatory mediators like TNF-α and other cytokines, ultimately causing severe hepatic injury (Yang et al. 2019).

According to this study, the positive control group's IL-10 level was also significantly higher than the negative control group's. Hepatocytes, sinusoidal endothelial cells, and Kupffer cells all contribute to producing the potent anti-inflammatory cytokine known as IL-10 in the liver. In chronic liver disorders, it is unmistakably linked to protective roles, and it is increased in several circumstances during liver inflammation (Hammerich and Tacke 2014).

Given that IL10 has been shown to protect the liver from drug-induced liver damage, the upregulation of IL-10 in this study was an accurate reflection of the liver's immunoreactive reaction to (APAP)-induced hepatotoxicity (Bourdi et al. 2002). This result is in line with earlier studies that looked at the hepatoprotective effects of carnosine and histidine on (APAP)-induced liver injury in mice and

discovered a considerable rise in IL-10 levels following high dosage (APAP) administration (Yan et al. 2009).

In the present study, a single dose of APAP caused damage to liver cells, which was linked to a significant increase in serum ALT and AST activity levels. In contrast, Omega 369 resulted in a significant decrease in these levels. This may be attributable to the anti-inflammatory properties of Omega 369. The present study's findings are consistent with previous research (Yoon et al. 2006; Forouzandeh et al. 2015; Majeed and Al-Shawi 2019).

Additionally, NAC at a dose of 100 mg/kg significantly attenuated the APAP intoxication-related increases in the activity level of these two enzymes. Elevated serum activity levels of AST and ALT have been linked to liver tissue dysfunctions since they are normally found in the cytoplasm and leak into the circulation as a result of cellular damage (Abdelkader et al. 2020; Al-Hussaniy et al. 2022; Al-Kuraishy et al. 2022; Naji et al. 2022). Normalizing these two enzymes' serum activity levels by Omega 369 suggests liver cell protection. Injury brought on by APAP's free radical metabolites (Aljuboury and Al-Shawi 2022; Mohammed and Hossain 2022) and the liver's defense against free radical production or antioxidant activity is crucial in preventing APAP-induced liver damage (Forouzandeh et al. 2013; Shaaban et al. 2023).

Pretreatment of mice with Omega 369 at doses of 50 and 100 mg/kg against APAP-induced acute hepatotoxicity suggests that Omega 369 mitigates liver damage through anti-inflammatory action. The increase of EPA and DHA reduces the concentration of arachidonic acid (AA) and lowers several series of inflammatory reactions (Ibrahim et al. 2021; Awad and Elsahar 2022).

Conclusion

According to this investigation's findings, it is clear that omega-3s have anti-inflammatory properties that prevent overall bodily damage when taken in moderation. Although some believe they are not always effective at preventing all types of damage, they decrease inflammation and lower the risk of bodily trauma. It can be inferred that Omega 369 can reduce signs of inflammation through significant reduction of TNF alpha , IL 10, ALT and AST levels in blood serum of mice.

Acknowledgments

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