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Hepatic detoxification activity of *Olea europaea L.* leaves against paracetamol-induced liver toxicity in rats

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Abstract

Hepatotoxicity is a critical impairment of liver caused by different reasons such as overdoses of some drugs like acetaminophen (paracetamol). The *Olea europaea L.* leaves have multiple pharmacological effects and may use as hepatic detoxification. 100 g of leaves powder has been macerated with 1000 ml absolute ethanol for 48 h., induction of hepatotoxicity in rats was done using 400 mg\kg of paracetamol, 25 mg/kg of silymarin was used as standard drug. Different concentrations ranged between 250, 500, 1000 and 2000 mg\kg of ethanolic extract were used to detoxing from rats liver. Liver enzymes (ALT, AST and ALP) have been measured after 24 h. of treatment. The results showed that the high level of (ALT, AST and ALP) has been reoptimized after treatment with different concentration. However, the concentration (2000 mg\kg) exhibited to regulate the liver enzyme better than other concentrations. We found that ethanol extract of *Olea europaea L.* leaves could act as hepatic detoxification agent in rats.

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Introduction

The liver is mainly responsible for the metabolism of exogenous and endogenous substances. It is playing an important role in the elimination and detoxification of drugs. Liver damage can be caused by malnutrition, xenobiotics, infection, alcohol consumption, anemia and therapies such as acetaminophen (paracetamol) (Mao *et al.* 2014). Paracetamol is one of the analgesic and antipyretic medicines which used widespread. If given at estimated doses it is considered a safe option. paracetamol is able to cause hepatic necrosis and death in overdoses (Bonkovsky *et al.* 1994). Most of patients who exposed to toxic dose of paracetamol presented with liver problems and increase in alanine amino transferase (ALT) and aspartate amino transferase (AST) levels within 24 h of drug exposure (Aycan *et al.* 2014).

The *Olea europaea L.* tree, known as olive, belongs to the Oleaceae family, and explored to has different pharmacological effects (Bianco and Ramunno 2006). Previous researches displayed that *Olea europaea L.* leaves have various phytochemical compounds such as phenols, maslinic acid, ursolic, oleanolic, quercetin, apigenin, luteolin, tannins, and caffeic acid etc. (Dekanski *et al.* 2009; Silva *et al.* 2006), as well as oleuropein, hydroxytyrosol, tyrosol and ligstroside (Guinda *et al.* 2015; Servili *et al.* 2009). Different biological and pharmacological effects were found in *Olea europaea L.* included wounds, hypertension, fever, atherosclerosis, diabetes, gout, antiarrhythmic, spasmolytic, immune-stimulant, cardioprotective as well as antivirals, antibacterial and antioxidants , in addition considered as good regulator of cholesterol levels in animals (Acar-Tek and Ağagündüz 2020; Lockyer *et al.* 2012) and treatment of obesity (Esmaeili-Mahani *et al.* 2010). The aim of this study was to evaluate the hepatic detoxification induced by paracetamol in rats using *Olea europaea L.* leaves extract.

Materials and methods

Plant collection

The fresh leaves of *Olea europaea L.* were collected from house garden, the leaves were authenticated by plant laboratory, college of sciences, University of Baghdad. The leaves have been well cleaned and rinsed in a dark place for 5 days at room temperature.

Olea europaea L. leaves extract

The dried leaves were grinded using blender. Subsequently, 100 g of leaves powder was dissolved in 1000 ml absolute ethanol and macerated for 48 h., thereafter the mixture was filtered and the product was concentrated using a rotary evaporator under reduced pressure (Dub and Dugani 2013).

The dark-green product was stored for further use. The yield % of extract was 17.8 %.

Animals

35 Wistar male rats (200–270 g) were involved in our study. The animals were kept in separated animal house with control temperature (24 ± 1.4 ◦C), (55-65 %) humidity and (12 h light\dark) cycle. The animals allowed access to water and food *ad libitum*, but restricted to fasting before 24 h of experiment starting. All animal procedures were in compactable accordance with the NIH Guide for the Care and Use of Laboratory Animals.

In vivo toxic induction and detoxification activity

The animals were divided into seven groups involving five rats in each group. Group I received distilled water only, group II received 400 mg/kg paracetamol only, group III received paracetamol 400 mg/kg + 25 mg/kg of silymarin (standard drug), group IV received paracetamol 400 mg/kg + 250 mg/kg of ethanolic extract, group V received paracetamol 400 mg/kg + 500 mg/kg of ethanolic extract, group VI received paracetamol 400 mg/kg + 1000 mg/kg of ethanolic extract and group VII received paracetamol 400 mg/kg + 2000 mg/kg of ethanolic extract.

The treatments were uninterrupted for 24 h. The blood samples were collected by puncturing retro-orbital plexus under simple ether anesthesia, serum was separated from whole blood by centrifugation for 2 min at 2000xg.

Biochemical analysis

To evaluate hepatic toxicity, activities of enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) levels were assessed by photometric method with an automated analyzer (Architect c16000; Abbott Laboratories, Abbott Park, IL, USA).

Statistical analysis

Data analysis was performed by using (GraphPad Prism version 6.04 for Windows, GraphPad Software, La Jolla California, USA). Data were expressed as mean ±standard deviation (SD). One-way ANOVA analysis of variance test was done. Result was considered significant at $P \leq 0.05$.

Results

Paracetamol acute toxicity and silymarin standard drug

The induction paracetamol (400 mg\kg) was done, level of (ALT) was elevated 120.8 ± 0.8 comparison with control 36.6 ± 0.7, the *P* value was < 0.001.

As well as, silymarin (25 mg\kg) was found to optimize the level of (ALT) 38.6 ± 0.4 comparison to control, the *P* value was = 0.230 (Figure 1).

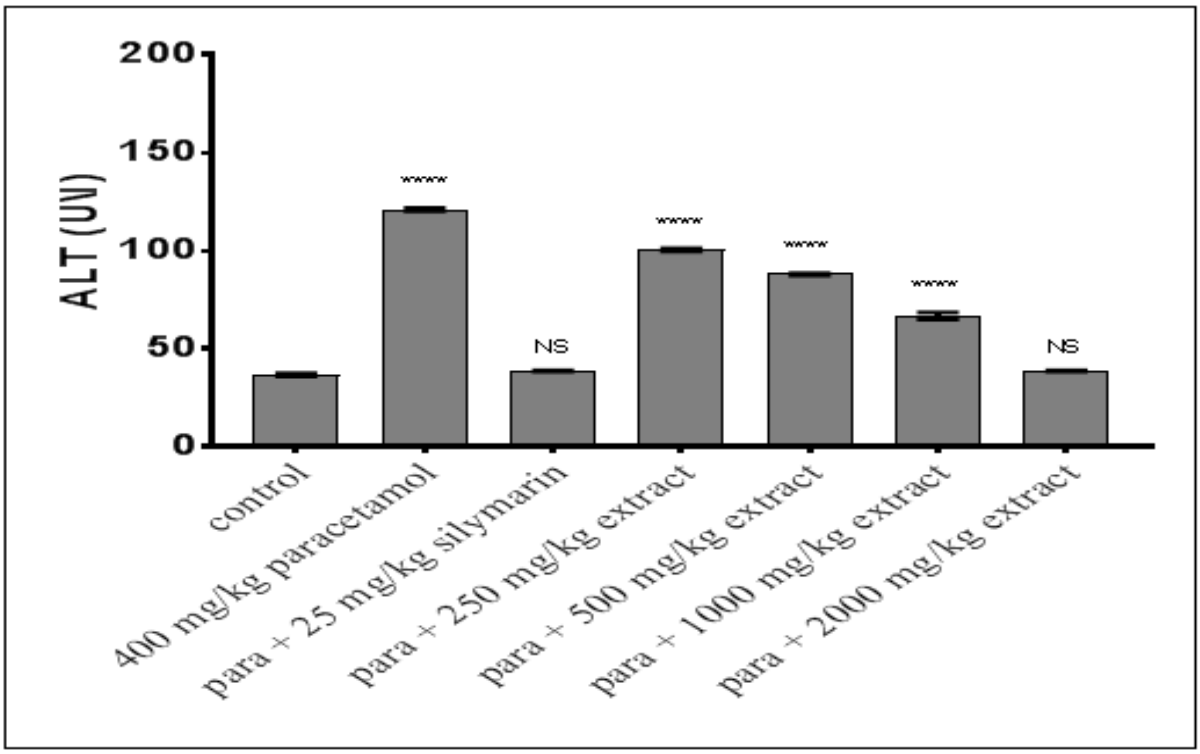

Fig. 1. Levels of (ALT) after treated with paracetamol, silymarin and different concentrations of extract. (****) refer to significance $P < 0.001$, while (NS) refer to non-significance.

(AST) Level was appeared to increase after treated with paracetamol (400 mg\kg) 165.5 ± 1.7 comparison to control 31.4 ± 1.4 and *P* value was < 0.001. Otherwise, silymarin (25 mg\kg) was appeared to regulate the level of (AST) 36.4 ± 5.2 comparison to control, the *P* value was = 0.186 (Figure 2).

Regarding to (ALP) level was found to rise after administrated with paracetamol (400 mg\kg) 251.7 ± 3.5 comparison to control 161.15 ± 0.3 and *P* value was < 0.001. On the other hand, silymarin (25 mg\kg) was displayed to adjust the level of (ALP) 163.7 ± 0.5 comparison to control, the *P* value was = 0.190 (Figure 3).

Ethanolic extract effect on (ALT) levels

The level of (ALT) was gradually regulated after treated with different concentrations of *Olea europaea L.* leaves extract. (250 mg\kg) 100.3 ± 0.8 and the *P* value was < 0.001, (500 mg\kg) 87.9 ± 0.5

and the *P* value was < 0.001, (1000 mg\kg) 66.55 ± 1.7 and the *P* value was < 0.001 and (2000 mg\kg) 38.7 ± 0.2 and the *P* value was = 0.187 comparison to control 36.6 ± 0.7 (Figure 1).

Effect of ethanolic extract on (AST) levels

The level of (AST) progressively controlled after administrated with different concentrations of *Olea europaea L.* leaves extract. (250 mg\kg) 123.9 ± 2.5 and the *P* value was < 0.001, (500 mg\kg) 78.3 ± 1.4 and the *P* value was < 0.001, (1000 mg\kg) 49.2 ± 0.4 and the *P* value was < 0.001 and (2000 mg\kg) 34.6 ± 0.9 and the *P* value was = 0.663 comparison to control 31.4 ± 1.4 (Figure 2).

Ethanolic extract effect on (ALP) levels

The level of (ALP) piecemeal adjusted after managed with different concentrations of *Olea europaea L.* leaves extract. (250 mg\kg) 231.8 ± 0.1 and the *P* value was < 0.001, (500 mg\kg) 210.0 ± 1.0 and the *P* value was < 0.001, (1000 mg\kg) 188.6 ± 0.4 and the *P* value was < 0.001 and (2000 mg\kg) 163.3 ± 0.6 and the *P* value was = 0.330 comparison to control 161.1 ± 0.3 (Figure 3).

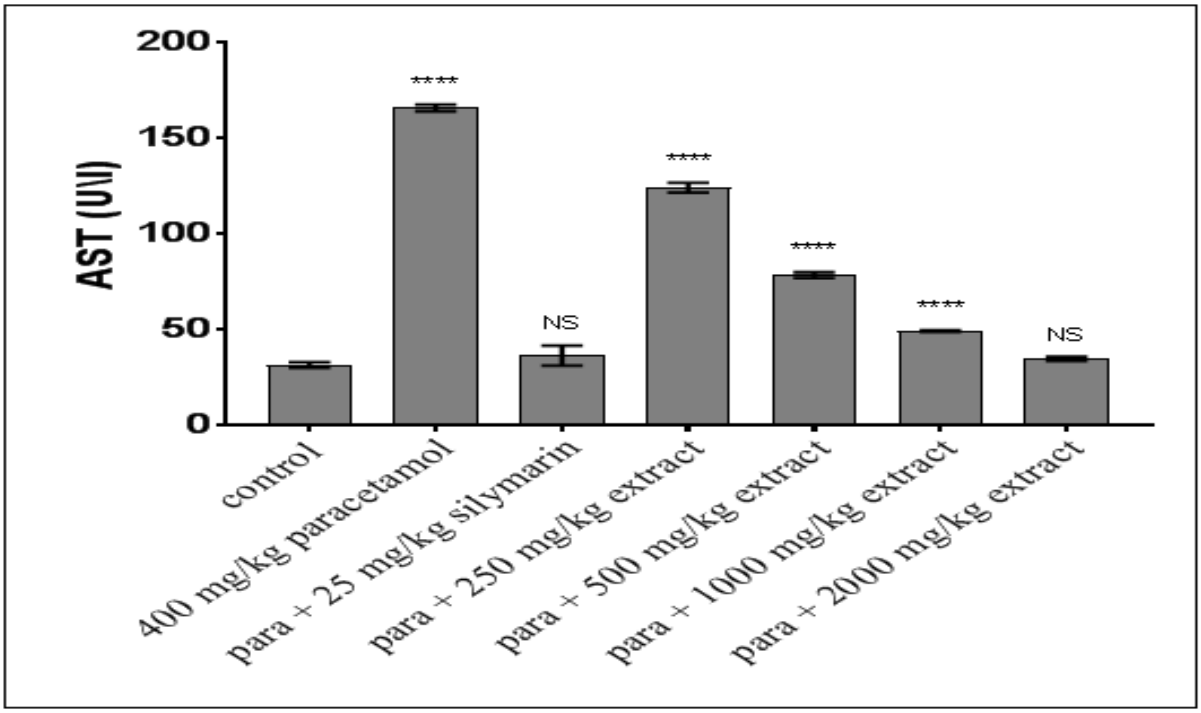

Fig. 2. Levels of (AST) after treated with paracetamol, silymarin and different concentrations of extract. (****) refer to significance *P* < 0.001, while (NS) refer to non-significance.

Discussion

The liver has many functions including maintain body homeostasis, metabolism, response to inflammation and detoxification (Tacke *et al.* 2009). Also, it's responsible on regulation of chemical environment of body.

Paracetamol is usually considered safe analgesia agent, nevertheless over doses of this drug lead to hepatic failure (Michaut *et al.* 2014). As well as, the toxic dose will lead to decrease in liver function which caused waste products aggregation like ammonia in blood (Mao *et al.* 2014).

The mechanism of paracetamol on liver is via toxic metabolite binding covalent, n-acetyl-p-benzoquinone-amine to the sulfhydryl group of protein resulting in cell necrosis and lipid peroxidation (Vivek *et al.* 1994). When damage to the liver cell plasma membrane occurs, a variety of enzymes that are stored in cytosol will be release into the blood stream. Increased serum enzyme production in the bloodstream has been linked with central submassive hepatic necrosis causing

significant hepatic injury (Venkatachalam and Muthukrishnan 2013).

Paracetamol often used as liver injury inducer model in hepatic detoxification drug survey and the liver injury is evaluated by rise of cytoplasmic enzyme level (AST, ALT, ALP, LDH, GGT) (Venkatachalam and Muthukrishnan 2013). However, these enzymes are considered as quantitative markers to develop the liver damage and function (Ansari *et al.* 1991).

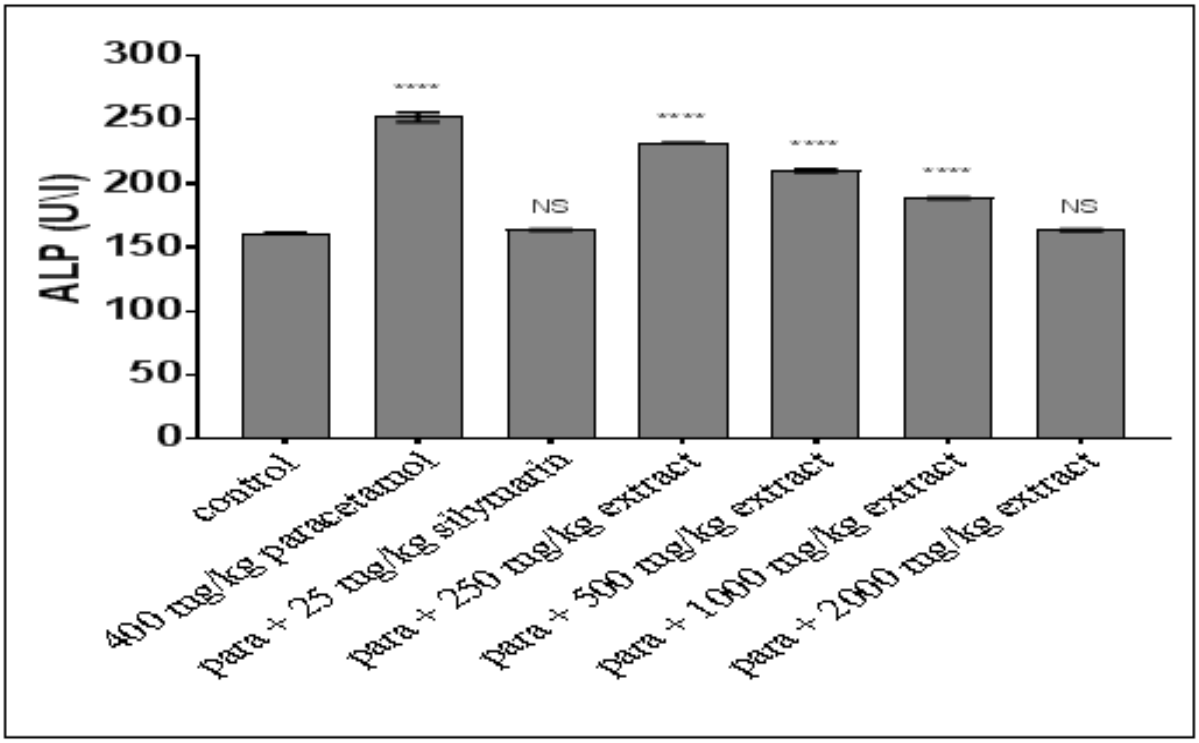

Fig. 3. Levels of (ALP) after treated with paracetamol, silymarin and different concentrations of extract. (****) refer to significance $P < 0.001$, while (NS) refer to non-significance.

Silymarin is a documented as hepatoprotective compound extracted from *Silybum marianum*. Additionally, it is found to have a protective effect on hepatocyte plasma membrane (Ramellini and Meldolesi 1976). Leaves ethanolic extract of *Olea europaea L.* as mentioned recently sound to have several phytochemical compounds (Dekanski *et al.* 2009; Guinda *et al.* 2015; Servili *et al.* 2009; Silva *et al.* 2006). The reduction in level of (ALT and AST) after induction of hepatic toxicity with paracetamol and these compounds suggested to repair of hepatic tissue damage. Furthermore, this effect suggested the serum transaminase levels return to normal with hepatic parenchyma enhancement and hepatocyte regeneration (Thabrew *et al.* 1987). As well as, the correction of (ALP) level supposed that the ethanolic extract preserved the membrane integrity of the hepatic cells, otherwise regulation of biliary pressure (Venkatachalam and Muthukrishnan 2013).

Conclusion

We conclude that ethanolic extract of *Olea europaea L.* leaves assumed to be a good natural antagonist which has hepatic detoxification effect. However, the study expects that higher concentrations could be more effective in regulation of liver enzymes than low concentrations.

Conflict of interest

There is no conflict of interest.

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