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Docking and in vivo study role of Kaempferoltargeting inflammatory mediators in hepatitis induced by Thioacetamide in Rats

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Abstract

Hepatitis is one of major serious liver disease that lead to decompensate liver cirrhosis. It caused by many factors as viruses, chemicals, life style and alcohol. Exploring the mechanism of hepatic injury in early stage can manage it and deceased mortality. Kaempferol (3,4′,5,7-tetrahydroxyflavone) is one of flavonoids present in many plants that used as folk medicine worldwide. Here, we investigated the mechanism of hepato-protective activity of Kaempferol against TAA (TAA) induced acute inflammation and hepatitis in rats. Six groups of rats were included (each 6 rats) were used ; Control, TAA intoxicated (500 mg/kg s.c.) for successive 15 days, TAA + Kaempferol (20 mg/kg treated) and TAA+ kaempferol (40 mg/kg treated), TAA + Kaempferol (20 mg/kg protected) and TAA+ kaempferol (40 mg/kg protected) . Serum liver function (ALT, AST, ALP, GGT) , malondialdehyde (MDA) , reduced glutathione (GSH), glutathione peroxidase (GSH-Px), glutathione S- transferase (GSH-T) and inflammatory mediators (NO, IL-6 and TNF-α), glutamate dehydrogenase (GLDH), malate dehydrogenase (MDH), and Paraoxonase 1 (PON1) were evaluated. Results obtained showed that, TAA increased of liver enzymes ($p<0.001$), MDA, NO, TNFα, IL-6 ($p<0.001$) levels versus control. In addition, reduced the activities of GSH-Px, GSH-T, GSH and non-significant changes in GLDH and MDH ($p<0.001$) and elevation of PON1 ($p<0.001$) versus control. Kaempferol administration protected against these abnormalities by suppressing production of inflammatory mediator ($p<0.001$) and stimulate antioxidant activities ($p<0.001$). In conclusion, it was suggested that, Kaempferol possesses antioxidant and anti-inflammatory effects against hepatitis induced by TAA. The protected effect is more potent than treated. Docking study showed that, Kaempferol exert strong specific binding to inflammatory receptors -8 ATP.

Keywords*:*Hepatitis, thioacetamide, Kaempferol, oxidative stress, paraoxonase 1, rats..

1. Introduction

The liver has a major physiological function as metabolism, synthesis, detoxification and secretion. Liver injury can be caused by many factors as pollution, drugs and infection. This injury can lead to fibrosis and hepatic dysfunction [1]. Malate dehydrogenase (MDH) is an important enzyme in the energy metabolism of eukaryotes while glutamate dehydrogenase (GLDH) is important for ammonia metabolism. Paraoxonase-1 (PON1) is aryl esterase enzymes has different function as anti-atherogenic agent, hydrolysis of organophosphate pesticides, statin and lactones [2]. Thioacetamide (TAA) is a thio-sulfur compound used in different industrial purposes as a fungicidal agent in textile products and motor oil stabilizer [2]. It was reported that, TAA can be used in experimental animals for induction of hepatitis, fibrosis and cirrhosis. When TAA administrated orally for long period, it causes biochemical and histological alterations similar to viral hepatitis infection [3]. The toxicity of TAA poisoning is due to bioactivation by oxidase system and CYP2E1 [4]. After activation, it produces reactive radicals' oxygen species (ROS) that bind to cellular components caused oxidative stress and dysfunction [5].There are no completely effective medications that support hepatic recovery without side effects. Natural products as phytochemicals are widely used in treatment of many abnormalities caused by oxidative stress [6]. Up till now, there are different protocols for management of hepatitis but some supplements can reduce complications. Flavonoids are structural and functional diverse family of secondary natural products impinging on the sessile life style [7]. The presence of plant flavonoids in human diets improve human health in different conditions as antioxidant [8]. Flavonoids include flavanones, flavones, flavanols, flavanols, flavan-3, 4-diols, catechins, proanthocyanidins and anthocyanidins [9]. One of these showed high activity is kaempferol that widely distributed in many foods as broccoli, grapefruit and tea [10]. It play a role in the attenuation of disease progression as apoptosis [11]. In addition, kaempferol showed no toxicity to normal cells so, it is safe as supplement without side effects [12]. Previous study stated that, kaempferol showed wound-healing activity in vivo in non-infected animals Soib et al. [13]. Kaempferol was found to exert antidiabetic and antimicrobial actions .Previous studies showed that apigenin had chemoprotective, hepatoprotective, in chemically induced hepatic damage [14,15]. This study evaluated the protective and therapeutic effects of Kaempferol in TAA-induced hepatotoxicity rat model by determination

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metabolic enzymes (malate dehydrogenase and glutamate dehydrogenase), ani-atherogenic enzyme (paraoxonase), oxidative stress, inflammatory markers and molecular docking to identify the possible mechanism of action.

2. Methodology.

2.1 Experimental design.

The handling of animals was done according to approval from ethical committee of King Abdulaziz University under number (KAU-BIOC-1081-24). Thioacetamide (TAA) was obtained from Fluka company, purity (99.2%). Thirty six male Sprague Dawely rats were supplied by animal house, KAU .The animals was kept at 25±2 ◦C. Animals were free access to standard diet and water.

Animals were allocated into six groups (n = 6 each). Group I (control); Group II rats were given dose of TAA in DMSO daily (200 mg/kg b.w) for successive 15 days. Groups III and IV were given TAA (200 mg/kg b.w) for successive 15 days and treated with kaempferol (20 or 40 mg /kg/day) respectively. Protective mechanism; Groups V and VI treated kaempferol (20 or 40 mg /kg/day) for 2 week and administrated TAA from second week. Animals were fasted, Blood and serum were separated and liver samples were dissected out. One gram of liver was homogenized in 5 ml PBS, pH 6.7 in ice using Teflon homogenizer, centrifuged for 15 minutes at 10,000 RPM, the supernatant was stored in -40℃ for analysis. Dose of TAA was given according to Seemaetal.,[16]. Doses of kaempeferol were given according to Inasetal., [17].

Serum was used for the determination of liver enzymes transaminases (AST,ALT,ALP,GGT), total protein, albumin and by colorimetric kits from Bio-diagnostic

2.2. Preparation ofLiver homogenate.

Liver was removed and washed from blood with ice-cold normal saline and homogenates (10%, w/v) was prepared in PBS (50 mmol/l, pH 7)[18]. The homogenate was used for evaluationmalondialdehyde, the reduced glutathione , glutathione peroxidase[19],glutathione-*S*-transferase. In addition the levels of NO , IL-6 and TNF-α were assayed in the liver homogenate. In addition the activity of Glutamate dehydrogenase (GLDH), malate dehydrogenase (MDH) and paraoxonase 1 (PON1) using ELISA kits from Bio diagnostic.

2.3. Determination of malondialdehyde (MDA).

The level of MDA was determined by thiobarbituricacid according to [20].

2.4.Determination of glutathione (reduced).

The GSH level was evaluated by the colorimetric assay method according to [21]. Theconcentrations wasexpressed as µmol/g protein.

2.5. Determination of glutathione peroxidase activity.

It was measured by the method described by Paglia and Valentine [22].

2.6.Determination of GST activity.

The activity of glutathione-*S*-transferase (GST) was assayed according to the procedure described by Habig *et al.* [23]. the activity of GST was estimated by using [9.6 mM^{-1} cm^{-1}] as the molar extinction coefficient for GST.

2.7. Determination of nitric oxide (NO).

The NO level was determined indirectly by measuring level of nitrite by a calorimetric method according to Griess reaction [24].

2.8. Determination of TNF-α and IL-6.

The concentration of TNF-α and IL-β in the liver homogenate were assayed by ELISA. From Biodignostic.

2.9. Molecular docking study.

It was be done using software computerized program me for bioinformatics.

2.10. Statistical analysis.

Data were analyzed for significance using SPPS version 22. ANOVA one awy was used, and if $p<0.05$ was considred significant.

3. Results.

Statistical analysis of data in (figs 1a-1f) showed that, TAA caused a significant elevation in the activities of liver enzymes ALT, AST, ALP and GGT ($p<0.001$) and non-significant changes in serum protein and albumin versus control. However, kaempferol at a dose 20 or 40 mg/kg b.w significantly normalize these elevation versus untreated. The protected trail is better than treated one. It was found that, TAA given rats significantly decreased GSH-Px activity and stimulate of GST activity ($p<0.001$) versus control. On other hand, protected with Kaempferol abrogated these changes better than treatment. Kaempferol decreased lipid peroxidation by lowering formation of MDA induced by TAA ($p<0.001$) (table 2). In addition, Kaempferol enhanced antioxidant capacity by elevation level of GSH reduced and antioxidant enzymes activities versus untreated. It was found that, TAA caused significantly increased in MDA level and lowered GSH in liver tissue as compared with control group (fig 2a, 2b). Administration of kaempferol at different doses significantly and dose dependently decreased the MDA level and elevated GSH level as compared with untreated group. Also TAA treatment decreased GSH-px activity versus normal group (fig2c). Treatment of rats with kaempferol resulted in a marked restoration of GSH-px activity versus untreated rats ($P<0.05$). the increased activity of GSH-px was found to be dose dependent. A significant and dose dependent increase in GST activity with kaempferol versus TAA ($P<0.001$) (fig 2d). Data obtained in fig (3a), revealed that, the level of serum NO was significantly elevated in rats injected with TAA. Administration of kaempferol corrected these effects by prevention the elevation of NO in the rats given different doses and show dose dependent manner. In addition, the levels of liver homogenate

TNFα and IL-6 were significantly elevated in TAA injected rats (fig 3b,3c).The elevated levels of TNFα and IL-6 were significantly and dose dependently reduced as a result of kaempferol administration. The effect was dose dependent ($p<0.001$). It was found that, TAA doesn't affect the activities of GDH (fig 3d) and MDH (fig 3e) versus control but elevated activity of PON1 ($p<0.001$) versus control. The protective showed better than treated group (fig 3f).

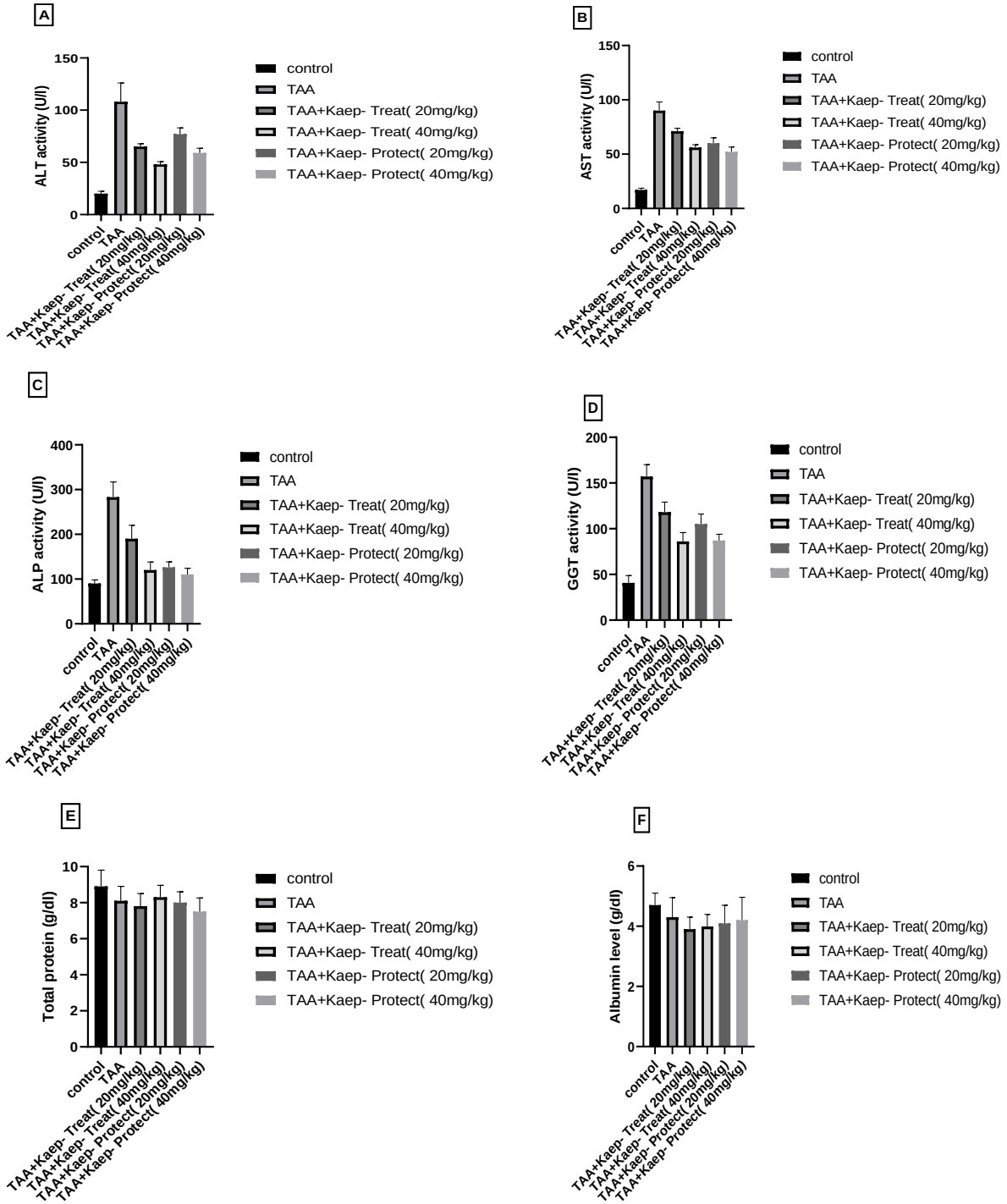

Fig (1): Liver functions test in all studied groups (mean ±SD). (A):Alanine transaminase; (B):Aspartate transaminase, (C): Alkaline phosphatase, (D): Gama glutamate transaminase, (E): Total protein, (F): Albumin.

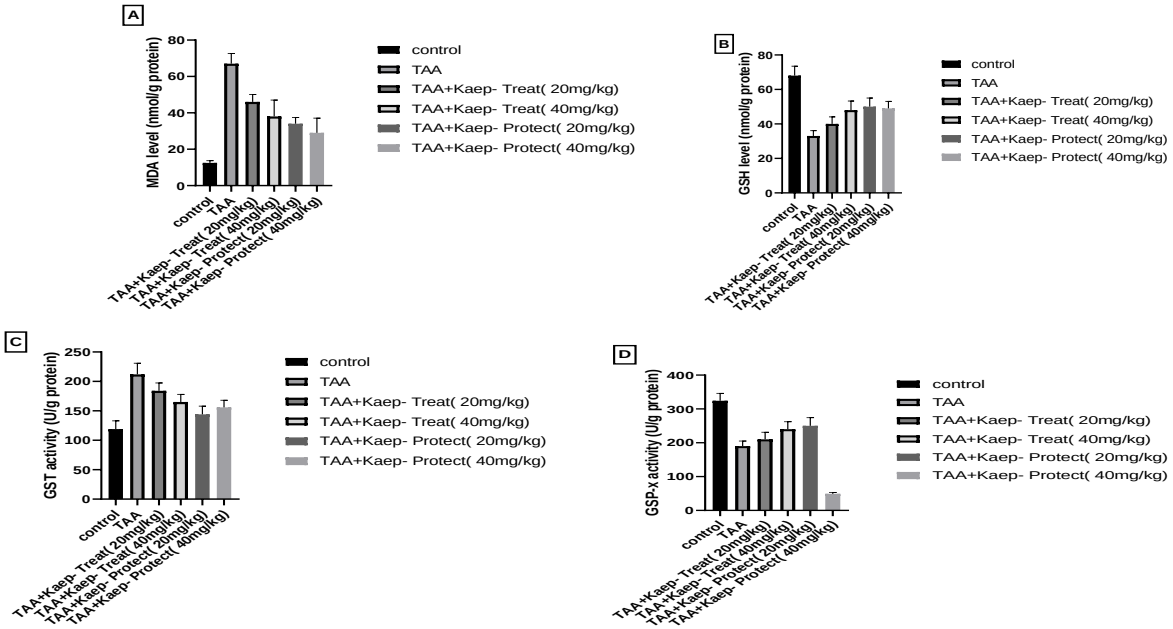

Fig (2): Oxidative stress markers in all studied groups. (A): Malondialdhyde, (B): reduced glutathione, (C): glutathione s-transferase, (D): glutathione peroxidase.

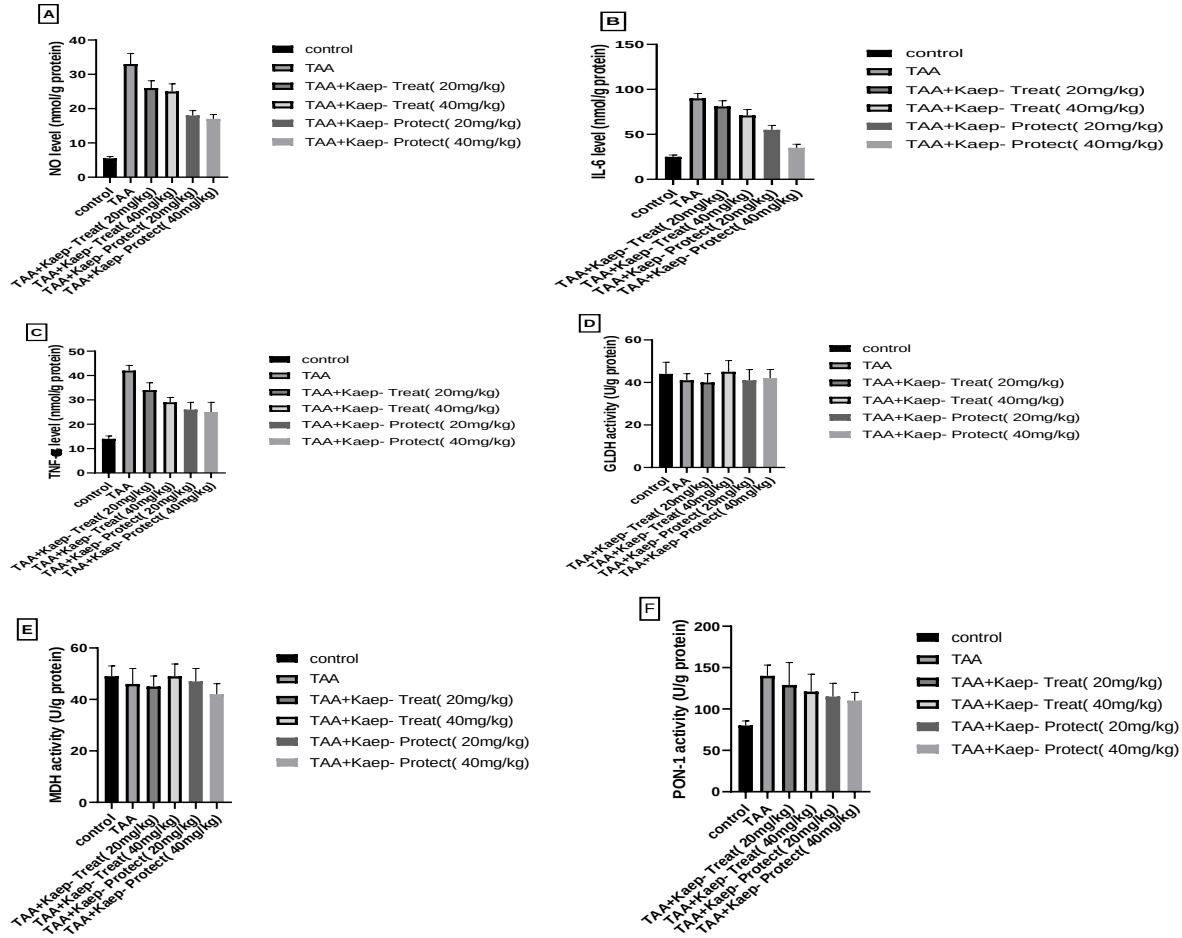

Fig (3): Inflammatory markers in all studied groups. (A): Nitric oxide level, (B): Interleukin -6 level,(C): tumor necrosis factor level ,(D): Glutamate dehydrogenase activity,(E): malate dehydrogenase activity,(F): paraoxonase-1 activity.

4. Discussion.

One of a fungicidal agent used in textile products is thioacetamide (TAA) but its limitation due to its hepatotoxicity [25]. It produce free radicals as TAA-S-S-sulfoxide. These radicals subsequently responsible for necrosis, fibrosis and liver damage [26,27]. The liver enzymes (ALT,AST,ALP, GGT) were statistically elevated in TAA injected rats. It was released as first indicatorof liver damage. Rats treated or protected with kaempferol showed a significant reduction in these enzymes compared with untreated. The protected is better than treated. The hepato-protective effect of kaempferol may be due to its protective effect of cell membrane from free radical damage caused by TAA [28]. The hepatic cytoplasm contains high levels of ALT and AST. The leakage of cytosol as TAA injected resulted in elevation in serum [29]. In the present study, the capability of kaempferol in controlling the TAA-induced hepatotoxicity was observed in that the animals treated with different doses of kaempferol showed dose dependent in the protection against this elevation when compared with the untreated animals. In vivo, treatment increases lipoperoxidation in the rat liver and in transplanted patients [30]. It was found that, plasma LDH, ALP and GGT were significantly elevated in TAA injected rats. However, this elevation returned to reach a normal level in treatment with kaempferol and dose dependent, so Kaempferol may act as a protective against damage effect hepatotoxicity.

For that, TAA can be used for induction hepatotoxicity for developing a new therapeutic agent [31].The free radicals caused by TAA indicated by elevation of MDA level and reduced antioxidant enzymes activity. Flavonoids are powerful scavenger agent of free radicals and prevent pathogenesis of hepatic disorder [32]. TAA was found to induce release of transaminases enzymes, abnormalities in coagulation process [33]. In addition, it stimulates production of ROS and oxidative damage [34]. Presence of free radicals increased probability for lipid peroxidation and MDA formation. This is the main reason for hepatic injury and release of intracellular enzymes to blood stream. Treatment or protection with kaempferol prevent production of free radicals and potentiate antioxidant activity, thus protect hepatocytes from injury. This is in accordance with study [35].

The main characteristic hallmark of hepatitis was shown to activate lysozymes, and hence increase cytokines secretion like IL-6 and TNF-α [36].*Kupffer* cells is a type of protective mechanism against foreign agent, and stimulate release of inflammatory agents to alert macrophage to engulf these molecules. In response to TAA, the TNF-α is released and subsequently other cytokines from macrophages for defense mechanism [37]. NO is a biphasic molecule that forming peroxynitrite and vasodilator [38]. In addition, the level of IL-6 was lowed by Kaempferol as a protective mechanism. TNF-α is a pro-inflammatory cytokine in diseases[39]. Following its release, it potentiates both inflammation andfree radical release [40]. It was reported that, production of nitric oxide by iNOS can result in hepatic injury [41].While the overproduction of iNOS is related with the acute liver injury in rats. This explained thatiNOShelp in the liver toxicity [42].

As indicated in our data, the elevated MDA level in rats injected with TAA and reduced antioxidant enzymes activities GST, GPx and reduced glutathione. Functional foods containing flavonoids are potent antioxidant by donate hydrogen to scavenger oxygen radicals. For that, stop radical chain reactions [43]. In the current study, protective or treated effect of with kaempeferol significantly enhanced the reduced glutathione, GST and GSPx, protecting the liver from radicals produced by TAA. It was suggested that kaempferol exert its action may be its antioxidant effects.In the current study, the hepato-protective effect of kaempferol not only attributed to its anti-inflammatory against NO, TNF-α, and IL-1β, but also to its antioxidant activity. This is in line with other previous data [44].The protective effect of kaempferol against hepatoxicity is dose dependent and showed suppression of inflammatory mediators. The limitations of this study; Kaempferol was limited to epigenetic study, should also be investigated in nanoparticles. The effect on other proteomics, genomic and metabolomics.

The decreased activity of SOD and CAT in TAA injected rats could be a consequence of inhibitory effects due to excess of ROS production . SOD is inhibited by hydrogen peroxide [45], and CAT by an excess of superoxide radical [46] and enhances formation of ROS, in turn [47]. It has been shown that reduces the content of protein sulfhydryl groups and causes protein thiol oxidation in rat liver cells [48], probably due to the -induced GSH depletion[48]. Malate dehydrogenase (MDH) catalyses the conversion of oxaloacetate and malate which important in Krebs cycle and the malate/aspartate shuttle (MAS) through the mitochondrial membrane.TAA injected rats doses not affect activity of MDH and GLDH that indicated these enzymes are mitochondrial origin and not affected first during toxicity. However, Paraoxonase 1 was significantly elevated in TAA injected rats versus control. However, kaempferol (20 or 40 mg/kg) showed reduction of paraoxonase versus untreated.This results opposite to other study who revealed that paraoxonase was reduced in acute or chronic hepatitis. The antioxidant properties of Kaempferol is attributable to its ability to quench reactive oxygen species. Kaempferol has a potent hepatoprotective activity against TAA-induced liver injury in rats.

5. Conclusion

Overall, Kaempferol not only prevented TAA-induced hepatic inflammation but also enhance antioxidant properties. The possible mechanisms is to maintenance of intracellular level of immunomodulator.

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8. Conflict of interest: The authors declare that; they have no any conflict of interest.

9. References.

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