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Biochemical evaluation of the protective effects of dandelion and safflower compared to silymarin against thioacetamide in rats.

Sara S. Elhefny[1], Fatma A.Gad[2], Alshaimaa M. Said[1]*

[1]*Biochemistry and Molecular Biology Department, Faculty of Veterinary Medicine, Benha University, Egypt.*

[2]*Clinical Pathology Department, Faculty of Veterinary Medicine, Benha University, Egypt.*

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ABSTRACT

The liver and kidneys play essential roles in detoxification, metabolism, and maintaining internal homeostasis; however, exposure to hepatotoxic and nephrotoxic agents such as thioacetamide (TAA) leads to tissue damage. This research focused on evaluating the protective potential of dandelion and safflower compared to silymarin. Liver and kidney injury was experimentally induced in rats using thioacetamide (TAA). A total of thirty-five rats were randomly divided into five groups. The control group received only a standard diet without any additional treatment. The TAA group was administered intraperitoneal injections of thioacetamide at a dose of 200 mg/kg body weight, twice a week, for a period of eight weeks. The remaining three groups were treated similarly with TAA, but in addition, each received one of the following oral treatments on a daily basis: silymarin (37.5 mg/kg), ethanolic extract of dandelion (200 mg/kg), or safflower extract (100 mg/kg). At the end of the experimental period, blood samples were collected to assess liver and kidney function markers. The findings demonstrated that TAA exposure caused a marked elevation in liver enzyme activities and renal function indicators, accompanied by a notable reduction in albumin levels compared to the control group. All treatments significantly ameliorated these parameters relative to the TAA group. Silymarin was more effective than dandelion in improving liver and kidney functions. Notably, safflower is more effective than both silymarin and dandelion in reducing the harmful effects of TAA on liver and kidney functions. These findings suggest that natural plant extracts such as dandelion and safflower may offer effective protection against TAA-induced liver and kidney damage.

1. INTRODUCTION

The liver is a vital organ that performs a wide range of physiological functions, such as the secretion of bile, the synthesis of plasma proteins, the regulation of nutrient absorption, the detoxification of harmful compounds, the modulation of immune responses, and the storage of essential vitamins (Kubes & Jenne, 2018). In addition, it plays a central role in maintaining the balance of carbohydrates, proteins, and lipids within the body (Williams et al., 2017). Many chronic disorders, including viral hepatitis and metabolic diseases, may cause continuous hepatic injury and inflammation (Higashi et al., 2017). During liver damage, the death of epithelial cells and activation of phagocytic cells lead to the release of inflammatory mediators, which subsequently trigger inflammatory cascades. Hepatic stellate cells (HSCs) represent the principal source of myofibroblasts that secrete extracellular matrix proteins and thus accelerate the process of liver fibrosis. When activated, HSCs undergo structural and functional modifications, including the expression of α-smooth muscle actin (α-SMA) and an overproduction of type I and type III collagens. This abnormal accumulation of extracellular matrix components disrupts the liver's normal tissue architecture, reduces its physiological efficiency, and may eventually progress to liver failure with serious clinical outcomes (Friedman, 2008).

Thioacetamide (TAA) is an organosulfur compound widely used in experimental research to induce hepatotoxicity, carcinogenesis, and hepatic fibrosis (Bashandy et al., 2020). Its metabolites are partially eliminated by the kidneys; therefore, efficient renal clearance is required to prevent systemic toxicity. Inadequate excretion can lead to accumulation of sulfoxide and disulfoxide derivatives, which intensify hepatic and renal injury. Thus, chronic administration of TAA imposes a dual toxic effect on both the liver and kidneys (El-Tantawy et al., 2019). In experimental animals, particularly rats, TAA is metabolized into acetamide and thioacetamide-S-oxide. The latter binds to cellular macromolecules, disrupts cell membranes, alters calcium regulation, and impairs mitochondrial activity, ultimately resulting in hepatocyte damage and death. TAA-induced liver fibrosis in rats has been shown to be irreversible and closely resembles the pathological changes observed in humans, which makes this model highly valuable for assessing potential antifibrotic therapies (Abdel-Rahman et al., 2021).

Recently, attention has shifted toward the utilization of natural and herbal remedies as complementary or alternative approaches for the management of liver disorders. Unlike many conventional drugs, which may have undesirable side effects or inconsistent efficacy, natural products often demonstrate greater safety and cost-effectiveness. Among these, silymarin, a flavonolignan complex extracted from the seeds of *Silybum marianum* (milk thistle), has been

* Correspondence to: alshaimaa.said@fvtm.bu.edu.eg

extensively studied due to its strong antioxidant, anti-inflammatory, and antifibrotic properties. It supports hepatocyte regeneration, enhances protein synthesis, and protects cellular structures from oxidative damage, which explains its therapeutic role in liver diseases (Kumar & Chaiyasut, 2015).

Dandelion (*Taraxacum officinale*) is another traditional medicinal plant that has long been used to promote liver health. It contains a wide range of nutrients, including vitamins, minerals, dietary fibers, and essential fatty acids. Its pharmacological activities are mainly attributed to its rich phytochemical composition, which contributes to its antioxidant, anti-inflammatory, diuretic, and anticancer effects (Devaraj, 2016).

Similarly, *Carthamus tinctorius L.* (safflower), a member of the Asteraceae family, is recognized in folk medicine for its therapeutic applications. Its seeds are abundant in flavonoids, phenolic acids, and polyunsaturated fatty acids, which impart strong antioxidant, anti-inflammatory, anticoagulant, and immunomodulatory activities. Safflower has demonstrated remarkable hepatoprotective potential, not only by reducing oxidative damage and pro-inflammatory mediators but also by preserving renal function under toxic conditions. These pharmacological properties make safflower a promising candidate for dual protection of hepatic and renal functions (Kumar & Chaiyasut, 2015; Gautam et al., 2014).

Based on these considerations, the present study was conducted to evaluate and compare the hepatoprotective and nephroprotective effects of dandelion and safflower extracts in relation to silymarin, using a rat model of thioacetamide-induced hepatic and renal toxicity.

2. MATERIAL AND METHODS

2.1.Experimental animals

A total of thirty-five male albino rats, each weighing approximately 200 ± 30 grams, were utilized in this experiment. The animals were sourced from the Animal House at the Faculty of Veterinary Medicine, Benha University. They were maintained under standard laboratory conditions, including a controlled temperature of 21–24 °C, relative humidity not exceeding 60%, and a 12-hour light/dark photoperiod. Throughout the acclimatization period, which lasted seven days prior to experimentation, rats had free access to a standard diet and clean drinking water. The study protocol received ethical approval from the Faculty of Veterinary Medicine, Benha University (BUFVTM 33-09-22).

2.2. Chemicals

Thioacetamide (TAA) was obtained from Sigma-Aldrich (St. Louis, MO, USA). Dandelion and safflower samples were sourced from a local herbal store. Silymarin was acquired through PHARCO Pharmaceutical Company.

2.3. Experimental Design

The thirty-five rats were randomly divided into five experimental groups, with seven animals each (n = 7). Control group: maintained on a standard diet without any treatment. Thioacetamide group: thioacetamide is administered intraperitoneally at a dose of 200 mg/kg of body weight twice weekly for eight weeks, following the method of Ftahy et al. (2013). Silymarin group: received TAA as described above and daily oral administration of silymarin at 37.5 mg/kg body weight for eight weeks (Paget and Barnes, 1964). Dandelion group: treated with TAA as above, along with an oral dose of dandelion ethanolic extract (200 mg/kg body weight/day) for eight weeks (Pfingstgraf et al., 2021).

Safflower group: subjected to the same TAA regimen, supplemented with oral safflower extract at 100 mg/kg body weight/day for eight weeks (Park, Chan Hum, et al., 2019).

2.4. Blood Samples

Blood was obtained from the medial canthus of the eye using capillary tubes. The collected samples were centrifuged at 3000 revolutions per minute for 15 minutes to separate the serum, which was then preserved at −20 °C until biochemical analyses were conducted.

2.5. Biochemical Analysis

The concentrations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured following the method described by Huang et al. (2006). Albumin levels were determined spectrophotometrically according to the procedure outlined by Doumas et al. (1997). Blood urea and creatinine concentrations were assessed based on the protocols established by Kaplan (1984) and Schirmeister et al. (1984).

2.6. Statistical Analysis

The data were presented as mean ± standard error (SE). Statistical comparisons among groups were conducted using a one-way analysis of variance (ANOVA), followed by the Duncan post hoc test. Analyses were performed using SPSS software version 25 (SPSS Inc., Chicago, IL, USA), and differences were considered statistically significant at $p < 0.05$.

3. RESULTS

Our findings showed that rats injected with TAA had a significant increase in liver activities (ALT, AST) as shown in Figure (1A&B) and kidney function (urea and creatinine) as presented in Figure (1D&E), with a significant decrease in albumin concentration when compared to the control group (Figure 1C). In detail, ALT and AST increased by about 465% and 325%, respectively, compared to the control group. At the same time, albumin decreased by nearly 59%, while urea and creatinine increased by about 235% and 584%, respectively. Oral silymarin treatment markedly improved these parameters. ALT and AST activities were reduced by about 42% and 39%, respectively, compared to the TAA group. Albumin concentration increased by nearly 48%, while urea and creatinine decreased by about 35% and 31%, respectively

Dandelion-treated rats also showed improvements, but to a lesser extent than silymarin. ALT and AST were reduced by about 21% and 16%, respectively, compared to TAA, with only a 14% increase in albumin. Urea and creatinine decreased by about 13% and 8%, respectively, showing moderate protection. Interestingly, safflower treatment demonstrated the strongest protective effect. ALT and AST decreased by about 57% and 55%, respectively, compared to the TAA group. Albumin concentration increased by nearly 82%, while urea and creatinine levels declined by about 51% and 60%, respectively. According to our findings, silymarin is more effective than dandelion in attenuating the negative effects of thioacetamide (TAA) on liver and kidney functions. However, safflower proved to be the most efficient in restoring liver and kidney markers toward normal levels.

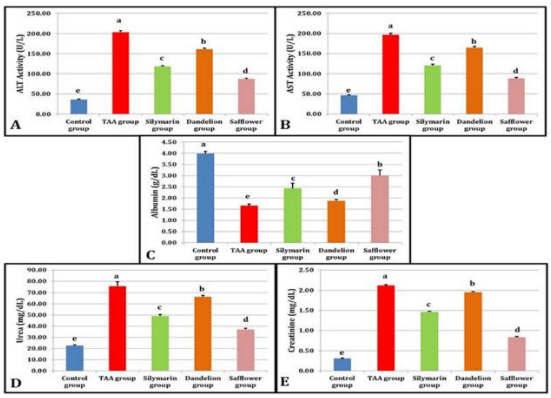

Figure 1: Biochemical evaluation of the protective effect of Dandelion, Safflower, and silymarin on liver and kidney alterations induced by TAA in rats A: ALT Activity (U/L); B: AST Activity (U/L); C: Serum Albumin level (g/dL); D: Blood urea (mg/dL); E: serum creatinine (mg/dL)

4. DISCUSSION

The liver is a vital organ involved in various physiological functions such as detoxification, bile acid synthesis, and the metabolism of macromolecules (Zheng et al., 2022). Upon metabolism, thioacetamide produces a hepatotoxic intermediate that triggers excessive generation of reactive oxygen species (ROS), contributing to the development of liver cirrhosis and fibrosis, which may eventually progress to hepatocellular carcinoma (HCC). This process is largely mediated by cytochrome P450 2E1 (CYP2E1), an enzyme essential for thioacetamide biotransformation (Bieche et al., 2007). According to the current study, rats were intraperitoneally injected with thioacetamide at a dose of 200 mg/kg body weight for eight weeks, which resulted in significant increases in hepatic enzyme activities in addition to a decrease in albumin when compared with the control group. These findings are consistent with those reported by Shareef et al. (2022) and Teksoy et al. (2020), who observed that intraperitoneal injection of TAA at 50 mg/kg to rats after 14 days or 200 mg/kg three times per week for two months induced increased liver activities. Elevations in serum enzyme activities could be attributed to their leakage into the bloodstream due to cellular injury reflecting hepatocyte membrane damage and cytoplasmic content release (Contreras-Zentella and Hernández-Muñoz, 2016). This may be ascribed to thioacetamide, a hepatotoxic compound that induces the generation of free radicals during metabolic breakdown, leading to oxidative stress, severe hepatitis, and programmed hepatocyte death (Elnfarawy et al., 2021). Similarly, El-Baz et al. (2021) associated elevated liver enzyme levels with oxidative stress and lipid peroxidation triggered by TAA's toxic effects. Free radicals damage lipids, proteins, and DNA, resulting in hepatocellular insult and necrosis. Necrotic cells frequently release their contents into the bloodstream, elevating transaminase activity. TAA metabolites, such as acetamide, sulfate, and sulfoxide-derived compounds, exert toxicity by increasing intracellular calcium and expanding nuclear volume, altering membrane permeability, inhibiting mitochondrial function, and ultimately inducing cell death. (Yamate et al., 2016). Additionally, TAA significantly reduced the albumin in this study, which could indicate damage to the liver cells and a decline in hepatic albumin production (Ramadan et al., 2018). TAA-S-oxide binds to large molecules, reducing cellular permeability and conductivity degradation through an effect on calcium stores. Hypoalbuminemia induced by TAA reflects compromised hepatic synthetic function and may predispose to renal dysfunction and increased mortality (Afshinnia et al., 2016). In this study, rats that were intraperitoneally injected with thioacetamide (TAA) at a dose of 200 mg/kg for eight weeks exhibited significant alterations in renal function, as evidenced by elevated serum levels of urea and creatinine. These findings are consistent with previous studies by Al-Attar et al. (2017) and Keshk et al. (2019), which reported marked nephrotoxicity following TAA administration. The observed renal dysfunction is likely attributed to the accumulation of TAA metabolites in renal tissues, which induce oxidative stress, impair glomerular filtration, and initiate tubular or interstitial damage (El-Tantawy et al., 2019). Furthermore, TAA has been shown to disrupt Na^+/K^+-ATPase activity and cause detachment of epithelial cells from renal tubules, ultimately leading to nephropathy and parenchymal injury (Birkner et al., 2008). Conversely, the co-administration of silymarin alongside TAA led to a notable improvement in liver function parameters compared to the TAA group alone, in agreement with the findings reported by Shelbaya (2013). Silymarin (22 mg/kg) significantly reduced liver enzyme activities and prevented fibrosis and hepatic necrosis induced by carbon tetrachloride, according to Abdel Salam et al. (2007). Its hepatoprotective effects are attributed to free radical scavenging, reduction of reactive oxygen species (ROS), maintenance of membrane integrity, and inhibition of mitochondrial apoptosis. Silymarin also suppresses the activation of hepatic stellate cells, limits pro-inflammatory cytokine production by hepatic macrophages, and promotes liver regeneration. (Bijak, 2017; Hashem et al., 2021). Silymarin treatment significantly reduced urea and creatinine levels, suggesting an improvement in renal function. This effect may be attributed to silymarin's antioxidant and anti-inflammatory actions, which protect renal tubular cells from oxidative damage and enhance the glomerular filtration rate (Al-Malki et al., 2020). Additionally, silymarin modulates nitric oxide pathways and preserves renal histological architecture (Fallahzadeh et al., 2020). Treatment with dandelion also contributed to the reduction of liver enzyme levels and supported the restoration of albumin production, although its effects were less pronounced than those of silymarin. The hepatoprotective action of dandelion is primarily attributed to its richness in flavonoids and phenolic compounds, which are known for their potent antioxidant and anti-inflammatory activities (Devaraj, 2016). Previous research has indicated that dandelion extract can decrease hepatic lipid peroxidation and regulate detoxifying enzyme activity, thereby offering protection against oxidative liver damage (González-Castejón et al., 2012). The presence of bioactive phytochemicals with antioxidative, anti-inflammatory, and anti-carcinogenic properties likely underlies its therapeutic potential (Colle et al., 2012). Dandelion exerted moderate renoprotective effects by reducing serum creatinine and urea. The plant's diuretic activity enhances toxin excretion, while its anti-inflammatory properties protect against nephron damage (Amirghofran et al., 2010). Additionally, the administration of safflower ethanolic extract markedly improved the liver enzyme activities that were altered by TAA. Safflower seeds reduced fibroblast proliferation, fatty degeneration, necrosis, and hepatic edema. Albumin, an indicator of chronic liver injury and hepatocyte function, increased significantly, suggesting enhanced liver regeneration, necrosis, and hepatic edema. These results align with those of Li, Yanuo, et al (2017) Safflower improved antioxidant defenses by increasing both enzymatic and non-enzymatic free radical scavengers, likely due to its

content of polyphenols and flavonoids such as quercetin, phenolic acids, and caffeic acid (Gautam et al., 2014).

5. CONCLUSIONS

5.Conclusion

The growing reliance on natural products stems from their promising therapeutic properties and minimal adverse effects. The findings of this study strongly support the protective potential of both safflower and dandelion ethanolic extracts against thioacetamide (TAA)-induced hepatic and renal damage. Notably, safflower extract exhibited superior hepatoprotective and nephroprotective effects compared to dandelion. Future studies should incorporate comprehensive biochemical, molecular, immunohistochemical, and histopathological analyses to gain a deeper understanding of the underlying protective mechanisms.

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