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Effect of Natural Products of Some Herbs on Biochemical parameters in Rats

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ABSTRACT— Pistacia khinjuk is a plant that has long been utilized in common medicine to cure a variety of conditions. The aim of this study was to evaluate that Pistacia khinjuk fruit extract affected several biochemical markers in a rat model to examine whether it might be used in traditional medicine. The hydroalcoholic extract was prepared by air-drying the plant's fruits. A total of forty male rats were separated into eight groups, with one serving as a control group and the others as test groups. The test animals were given orally for twenty-eight days a 200 mg/kg dose of Pistacia khinjuk for group2, Sorafenib for group3, Alcoholic extract and Sorafenib for group4, CCl4 for group5, Alcoholic extract and CCl4 for group6, Sorafenib and CCl4 for group7, and Alcoholic extract, Sorafenib, and CCl4 group8. The biochemical data were analyzed with SPSS software and represented as means ± SD before being submitted to one-way analysis of variance (ANOVA) and post-hoc Tukey tests. PNO2 and GSH levels fell significantly ($p < 0.05$) in the CCl4 group compared to the control group, according to the results obtained for the specified biochemical parameters. When comparing the CCl4 group to the other groups, the levels of AFP and MDA rose considerably ($p < 0.05$). The fruit extract of Pistacia khinjuk exhibits hypocholesterolaemic qualities, a hepatoprotective impact, enhances GSH, PNO2, and decreases MDA, according to this study. hepatic disorders may all benefit greatly from this treatment.

KEYWORDS: Pistacia khinjuk, lipid peroxidation, medical plants, carbon tetrachloride

1. INTRODUCTION

The liver, which plays a key role in metabolism and excretion, is continually bombarded with a variety of xenobiotics and therapeutic medications. Every year, around 20,000 individuals die as a consequence of liver diseases, which are frequently caused by medicines, leading in glutathione depletion and oxidative stress, which leads to liver necrosis [18]. Natural antioxidant compounds, such as polyphenols found in medicinal plants, can protect the liver from the harmful side effects of modern drugs. Diabetes induces oxidative stress as a result of glucose oxidation, hence it's very important to preserve the liver of diabetics [37].

Industrial growth has a tainted essence. It is considered a toxic chemical [16]. Human inhales CCl_4 through the mouth, nose, and skin pores. It has a role in the event of CCl_4 contamination in large quantities from generating ROS in various tissues of the body, such as the liver and kidneys [29]. Its effect begins specifically with its association with liver cytochrome P450, which generates free radicals trichloromethyl (CCl3), which irritates the double bonds of phospholipids in cell membranes [1]. Continuing the persistent detrimental effect of Trichloromethylferoxyacetin (CCl_3O_2), with cellular proteins and lipids and its effect. On the permeable ability of mitochondrial organelles, endoplasmic reticulum and plasma walls, causing cell damage [30].

The damage caused by CCl_4 changes the amount of antioxidants in the body's cells and tissues that are affected by free radicals, leading to tissue denaturation, M, according to [5]. In other studies, CCl4 injection into laboratory animals resulted in elevated cholesterol, TG, and FFA levels in serum and liver and kidney tissues of laboratory rats, in addition to bone marrow genotoxic effects [13]. These factors lead to a decrease in endogenous antioxidants, and in turn, an increase in the proportion of free radicals [2]. Natural antioxidants have gotten a lot of press for their ability to defend against toxicity caused by chemicals. Herbalists are doctors that specialize in medicinal plants that have been proved to provide a wide range of health benefits in a variety of illnesses [26].

The Anacardiaceae family of wild herbs includes the wild pistachio or Khinjuk (Pistacia khinjuk). This plant is known as "khenjuk" in Iraq. Pistacia khinjuk trees can withstand the harshest of temperatures. Their natural habitats include Iraq, Turkey, Egypt, Syria, Iran, Afghanistan, and Pakistan. The fruits are blue and black, with golden seeds [8]. The use of P. khinjuk as a natural component in traditional Persian medicine has been recorded in several studies. Important medical uses include reducing nausea, maintaining balance in movement, stomach discomfort, and vomiting. P. khinjuk fruit extract is used, and due to the Kolkhoung extract containing a high percentage of secondary compounds of flavonoids and phenolic compounds, it is used in the manufacture of medicines and anti-medicines.

Its fruits and resins are believed to have antioxidant properties. Medicinal plants can affect biochemical parameters in a number of ways. As a result, the goal of this study was to see if ethanolic extracts from pistacia Khinjuk leaves might protect male rats' livers from carbon tetrachloride-induced liver damage.

2. Materials and Methods

2.1 Chemicals and materials

The carbon tetrachloride came from SISCO Research PVT LTD's Laboratories (Mumbai, India). BioLabo (French Private Limited) was approached for analytical grade kits and other materials. The leaves of the Konjuk tree (Pistacia khinjuk) were collected at the end of November of the year 2020 from the Matin Mountains in the Amadiyah district in the Dohuk governorate and placed in dry bags, then cleaned of dust and then placed in pots to be dried well on natural air for two weeks Then store it in paper bags for study. Plant classification sources for medicinal plants were used to provide a categorization to it. At the University of Mosul's College of Education's herbariums, a voucher specimen of the plant was also identified and recorded.

2.2 Pistacia khinjuk extraction

Gupt mardu et al. devised a process for extracting alcoholic extracts from the Pistacia khinjuk plant (Gupt mardu et al., 2012).

2.3 Experimentation on Animals

Male albino rats weighing 160 to 200 grams were sold by the University of Mosul's College of Veterinary Medicine. The animals were kept in normal cages with unrestricted food and water access (a typical laboratory pellet diet). The temperature in the animal habitat was regulated between 24 and 29 °C using a 12-hour light/dark cycle. The Institutional Animal Ethical Committee authorized the experimental protocol (IAEC).

2.4 Design Experimentation

Experimentation on Animals

Using forty rats, the protective function of Pistacia khinjuk against carbon tetrachloride-induced hepatotoxicity was examined. Animals (rats) were divided into (8) groups after determining the median lethal dose (LD50). Which was (0.2 ml/kg) for carbon tetrachloride of body weight and the dose of extract and drug was (200 and 30 mg/kg) of body weight respectively. The rats were divided into eight groups of five, with each group receiving the following treatments:

- The first group / the healthy control that is treated with water and protein feed only
- The second group (alcoholic extract): alcoholic extract received the dose orally daily.
- The third group / (Sorafineb): Sorafineb received the dose orally daily.
- The fourth group / carbon tetrachloride received the dose once by chelation injection (It is an area located between the thigh and abdomen).
- The fifth group / (alcoholic extract and medicine), which received the dose daily for mouth.
- Sixth group / (alcoholic extract and carbon tetrachloride), which received the daily dose for the extract and once for carbon tetrachloride.
- The seventh group / (the drug Sorafeneb and carbon tetrachloride) who received the daily dose of the drug and once for carbon tetrachloride.
- The eighth group (Sorafenib, alcoholic extract, and carbon tetrachloride) received a daily dose of the drug, alcoholic extract and one dose of carbon tetrachloride.

2.5 Biochemical analysis

Appreciation of Alpha Vito protein enzyme using a test (ELISA) applied by Pars Biochem (China). Serum Paraoxonase Enzyme Activity (PON) was estimated according to Tomas et al. method (2000), [10]. Malondialdehyde concentrations have been measured using thiobarbituric acid reactions (MDA). The [15], [4]. Technique was used to quantify the concentration of thiobarbituric acid (TBARS) in the tissue, and the [27] method was used to calculate GSH.

2.6 Quantification with HPLC-DAD and LC-MS/MS The Extracts' Characterization

Reversed phase HPLC analysis was used to quantify distinct phenolic chemicals, employing a SYKAMN HPLC chromatographic system equipped with a UV detector, Chemstation, and a Zorbax Eclipse Plus-C18-OSD. 4.6mm column, 25cm The temperature in the column was 30°C. The gradient elution technique was used using eluent A (methanol) and eluent B (1 percent formic acid in water (v/v)) as follows: 0-7 min, 80 percent B; 7-18 min, 60 percent B; and 1.1 mL/min flow rate.

The volume of samples and standards injected was 100 L, and it was done automatically with an autosampler. The spectra were taken at a wavelength of 280 nm.

2.7 Histological examination of the liver

Liver slices were collected immediately after dissection from the liver and were fixed in 10% buffered formalin [25], dried in progressive ethanol (50 to 100 percent), washed in xylene, and embedded in parafine. Photomircoscopic observations of cell necrosis, lipid change, hyaline degeneration, ballooning degeneration, and infiltration of kupffer cells and lymphocytes were made at 40X magnification and stained with Haematoxylin and Eosin (H and E) dye.

2.8 Analytical statistics

The data was analyzed using one-way ANOVA. Duncan's unique multiple range test was used to resolve the variation between treatment means. For all statistical research, the statistical tool SPSS 27.0 was employed (SPSS Ltd., Surrey, UK).

3. Results

Table 1 showed the effect of carbon tetrachloride and pistacia Khinjuk extraction on AFP, PNO_2, MDA, GSH, and MDA of rats males. Results revealed that AFP values in the CCl4 group, Alcoholic extract+CCl_4group, Sorafenib +CCl_4 group of male rats were higher (1.43±0.15, 0.94±0.15, 0.86±0.02) respectively than that of Alcoholic extract group, Sorafenib group, and Alcoholic extract+ Sorafenib group as 0.75±0.0 for each. See table 1.

Also, the results shows that PNO_2 in Alcoholic extract with Sorafenib group (2.92±0.01) was higher followed by Alcoholic extract group and Alcoholic extract with Sorafenib with CCl_4 group (2.86±0.02, 1.99±0.04) respectively. while the level of PNO_2 was lower in CCl_4 group and Sorafenib with CCl_4 group as (1.50±0.26, 1.67±0.10) respectively (Table 1). With tissue MDA, the results reveals that the higher level of MDA was 582.09±46.88 in CCl4 group, followed by Alcoholic extract with CCl_4 group, Sorafenib with CCl_4 group as (428.05±49.41, 424.21±29.15) respectively. while the lower level of tissue MDA was 267.3±36.77 in Alcoholic extract group compared to healthy control (394.48±30.11). our study showed the results of tissue GSH (nmol/gm). The results reveals that tissue GSH in control group (5522.52±90.40) was lower than Alcoholic extract with Sorafenib group, Alcoholic extract group, Alcoholic extract with Sorafenib with CCl_4 group, and Sorafenib with CCl_4 group as (7653.03±279, 7559.59±428.7, 6016.54±637.74, 5625.00±209.63) respectively. while the results shows that tissue GSH in CCl_4 group, Sorafenib group, and Alcoholic extract+CCl_4 group (2522.98±250.73, 3101.56±376.03, and 5242.19±199.01) respectively lower than control group (5522.52±90.40) (Table 1). Furthermore, the present study shows the results of Serum-MDA(mmol/l). The results reveals that S-MDA in control group (3.41±0.06) was lower than Alcoholic extract with Sorafenib group, Alcoholic extract group, Alcoholic extract with Sorafenib with CCl_4 group, and Sorafenib group as (5.27±0.41, 4.04±0.02, 3.60±0.17, and 3.44±0.34) respectively. while the results shows that S-MDA in CCl_4 group, Sorafenib with CCl_4 group, and Alcoholic extract with CCl_4 group (1.60±0.29, 2.61±0.48, and 2.68±0.32) respectively lower than control group (3.41±0.06) (Table 1). Moreover, our study shows the results of Serum- GSH(mmol/l). The results reveals that S- GSH(mmol/l) in control group (1.89±0.12) was lower than CCl4 group, Sorafenib with CCl_4 group, Alcoholic extract with CCl_4 group, Alcoholic extract with Sorafenib with CCl_4 group, and Sorafenib group as (4.26±0.05, 2.71±0.07, 2.19±0.16, 1.96±0.11, and 1.93±0.38) respectively. while the results shows that S- GSH(mmol/l) in Alcoholic extract with Sorafenib group and Alcoholic extract group (0.96±0.07 and 1.15 ± 0.25) respectively lower than control group (1.89±0.12) (Table 1).

Table 1: Effect of carbon tetrachloride and pistacia Khinjuk extraction on AFP, PNO_2, MDA, GSH, and MDA of male rats

Groups Parameters	Control group (mean ± SD)	Alcoholic extract group (mean ± SD)	Sorafenib group (mean ± SD)	Alcoholic extract+ Sorafenib group (mean ± SD)	CCl_4 group (mean ± SD)	Alcoholic extract+CCl_4 group (mean ± SD)	Sorafenib +CCl_4 group (mean ± SD)	Alcoholic extract+ Sorafenib + CCl_4 group (mean ± SD)
AFP	0.75±00a	0.75±0.0 a	0.75±0.0 a	0.75±0.0a	1.43±0.15c	0.94±0.15c	0.86±0.02b c	0.77±0.02a b
PNO2	1.74±0.0 4a	2.86±0.0 2 c	1.74±0.01 d	2.92±0.01 c	1.50±0.26 d	1.8±0.06a	1.67±0.10a	1.99±0.04 b
MDA(nmol/gm)	394.48±3 0.11a	267.3±36 .77d	356.4±25. 23 e	268.39±2 2.6d	582.09±46 .88c	428.05±49 .41b	424.21±29. 15b	396.85±56 .81a

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GSH (nmol/gm)	5522.52± 90.40 a	7559.59± 428.7 c	3101.56± 376.03 e	7653.03± 279.2c	2522.98±2 50.73d	5242.19±1 99.01a	5625.00±20 9.63ab	6016.54±6 3.774b
S-GSH(mmol/l)	3.41±0.0 6a	4.04±0.0 2 b	3.44±0.34 a	5.27±0.41 c	1.60±0.29 d	2.68±0.32 e	2.61±0.48e	3.60±0.17 a
S-MDA(mmol/l)	1.89±0.1 2 a	1.15 ± 0.25 e	1.93±0.38 a	0.96±0.07 e	4.26±0.05 d	2.17±0.16 b	2.71±0.07c	1.96±0.11 ab

External standards was used to quantify the indicated chemicals discovered in the leaves and fruits. Epicatechine (30.2841.9) was shown to be the most abundant component in the Alcoholic extract group, followed by Luteolin (30.056.48), Gallic Acid (14.08 0.004), Catechin (7.331.47), Apigenin (7.270.19), Rutin (4.360.88), and finally Qurcetine (3.8720.05). (Figure 4). in Alcoholic extract and Sorafenib group, Luteolin (37.9±0.09) was the higher quantity of phenolics, followed by Epicatechine (23.855±1.88), Gallic Acid (17.255 ± 0.398), Apigenin (10.05±0.88), Catechin (5.52±0.19), Qurcetine (5.40±0.011), and finally Rutin (4.89± 0.71) (Figure 2). in Alcoholic extract and CCl4 group, Luteolin (2.35±0.03) was the higher quantity of phenolics, followed by Epicatechine (1.496±0.003), Gallic Acid (1.075 ± 0.044), Apigenin (0.415±0.003), Catechin (0.24 ± 0.024), Qurcetine (0.206±0.002), and finally Rutin (0.182 ± 0.004) (Figure 3). furthermore, the results the higher quantity of phenolics in Alcoholic extract, Sorafenib and CCl4 group was Epicatechine (0.812±0.005), followed by Gallic Acid (0.733 ± 0.25), Luteolin (0.532±0.04), Catechin (0.214± 0.003), Apigenin (0.196±0.002), Qurcetine (0.082±0.009), and finally Rutin (0.08 ± 0.0008) (figure 5) (Table 2).

Table 2: Phenolics in ethanolic extracts: quantitative and qualitative analyses under varied treatment conditions.

Study groups / **Compounds**	**Alcoholic extract+ Sorafenib + CCl_4 group**	**Alcoholic extract+CCl_4**	**Alcoholic extract+ Sorafenib**	**Alcoholic extract group**	**Control group**
	Mean ± SD				
Gallic Acid	0.733 ± 0.25 e	1.075 ± 0.044 f	17.255 ± 0.398 c	14.08 ± 0.004 b	1.476 ± 0.17 a
Catechin	0.214± 0.003 a	0.24 ± 0.024 a	5.52±0.19b	7.33±1.47c	0.773±0.066a
Epicatechine	0.812±0.005 a	1.496±0.003 a	23.855±1.88b	30.284±1.9b	1.429±0.006 a
Qurcetine	0.082±0.009 e	0.206±0.002 b	5.40±0.011 d	3.872±0.05c	0.183±0.021 ab
Apigenin	0.196±0.002a	0.415±0.003a	10.05±0.88 c	7.27±0.19b	0.226±0.014A
Rutin	0.08 ± 0.0008 a	0.182 ± 0.004 a	4.89± 0.71 b	4.36±0.88b	0.177±0.03a
Luteolin	0.532±0.04 a	2.35±0.03 a	37.9±0.09 c	30.05±6.48b	1.154±0.04a

Figure 1: Retention time and Voltage of components in controls group

Figure 2: Retention time and Voltage of components in Alcoholic extract, and Sorafenib group.

Figure 3: Retention time and Voltage of components in group treated extraction and CCl_4

Figure 4: Retention time and Voltage of components in extraction treated group

Figure 5: Retention time and Voltage of components in Alcoholic extract, Sorafenib, and CCl_4 group.

The following observations were made using histological sections and the histological injury score (figure 6). There were no major structural abnormalities in the livers of rats exposed to subchronic treatment with different extracts conditions, according to histopathological investigations. In this study, Histological examination of the liver of a rat of the group treated with the carcinogen CCL_4 revealed the presence of hepatoma cells of various shapes and sizes as well as the presence of fibrous tissue and around the central vein. On other side, the Histological examination of rat liver in group treated with carbon tetrachloride and alcoholic extract showed sinusoids, vascular congestion and slight infiltration of inflammatory cells. With the drug-treated group only, Histological examination of rat liver shows normal histological features represented by hepatocytes with slight congestion in the sinusoids and central vein. While the histological examination of liver tissue of the control group showing normal histological through hepatocytes, sinusoids and central vein.

4. Discussion

The effects of pistacia Khinjuk alcoholic extract on CCl4-induced hepatotoxicity in adult male rats were examined in this study. In addition, the effect of the extract on liver function and oxidative stress indicators was investigated in this issue (hepatic glutathione reductase activity and malondialdehyde levels). Hepatotoxic and nephrotoxic effects of CCl_4 are well-known. The amount of toxicity is influenced by the overproduction of reactive oxygen species (ROS), oxidative damage, and the inflammatory process. Intoxication with CCl_4 produces free radicals like nitric oxide and peroxynitrite, which set off a chain reaction in rats that causes liver and kidney damage [21]. As a result, we found that liver MAD and AFP levels were significantly higher in the CCl_4-treated group, whereas GSH and PNO_2 levels were significantly lower. As previously reported, these findings hint to hepatocyte malfunction, cellular leakage, and a loss of functional integrity of the cell membrane in the liver [23].

On antioxidant enzymes in the liver, [36] found similar results. [38] found that CCl_4 is processed by cytochrome p450 (CYP2E1 isoform) producing trichloromethyl CCl_3• and Cl_3COO• (hepatotoxic radicals) that covalently bond to cell components, causing alteration in lipid peroxidation and antioxidant enzymes. LPO also triggers hepatic necrosis, inflammatory cell activation, including macrophage activation, HSC activation, and the release of fibrogenic mediators. The main causes of fibrosis advancement include an imbalance in oxidant/antioxidant state, as well as the liberation of lipid peroxide metabolites and inflammatory cytokines [34]. The term "oxidative stress" refers to a change in cellular redox homeostasis. Following CCl_4 treatment, we discovered a substantial rise in MDA and a considerable reduction in GSH enzyme activity in rat tissues. This is consistent with past research [21], [28]. MDA levels were reduced and GSH levels were enhanced after treatment with pistacia Khinjuk. The antioxidant properties of pistacia Khinjuk are attributed to three factors: (1) its chemical structure, which may directly scavenge ROS; (2) its capacity to boost GSH synthesis and the cellular defense system; and (3) its inhibitory action on xanthine oxidase, which produces ROS [24].

Furthermore, lipid peroxidation (LPO), which damages biomembranes, is a pathogenic process. It's thought to be an oxidative stress sign caused by an imbalance in the antioxidant and prooxidant processes. Increased MDA, a valid LPO marker, in the kidney and liver is linked to CCl4 exposure [7]. Following CCl4 treatment in animals, several studies have found an increase in MDA levels as well as a reduction in antioxidant levels such as SOD and GSH [32], [3]. The first line of defense against free radicals is reduced

glutathione (GSH). Hepatic cell damage was suggested by a decrease in liver GSH and a decrease in GPx activity in CCl4-treated rats. Through the participation of GPx, the availability of adequate GSH improved the detoxification of active CCl4 metabolites. The protective activity of the extract is compensated for by the restoration of GSH levels following the administration of plant extract to such CCl4-treated rats. According to [11] findings, plant extract treated groups have lower glutathione levels (2004). Apart from its traditional activity as a ROS scavenger by feeding on radicals, GSH has a number of other roles, including but not limited to serving as a cysteine reservoir [31]. In the onset and development of cancer, GSH acts as a double-edged sword. Moderate ROS levels have long been thought to have a role in cancer start and progression by causing mutations and boosting genomic instability, which leads to the activation of oncogenic signaling pathways that enhance cell survival, proliferation, and stress resistance [19].

Sorafenib, an FDA-approved kinase inhibitor, inhibits a variety of kinases, including cell surface tyrosine kinases (e.g., vascular endothelial growth factor receptor, VEGFR; platelet-derived growth factor receptor, PDGFR; tyrosine-protein kinase kit, KIT; Fms-like tyrosine kinase, Fms-like [22]. Because these kinases are involved in cancer cell proliferation, angiogenesis, and apoptosis, sorafenib has been shown to inhibit cancer cell proliferation and induce apoptosis in vitro, as well as prevent tumor growth in vivo [22]. Several investigations have recently demonstrated that sorafenib, but not other kinase inhibitors in the same class, exhibits new inhibitory action vs xCT, resulting in reduced cysteine absorption, GSH depletion, and ROS buildup, eventually leading to endoplasmic reticulum stress and ferroptosis [33]. Despite the fact that paraoxonases have a direct role in cancer cells, it may be worthwhile to look for alternative nearby roles. For the first time, PON2 [12] and PON3 [35] were revealed to impact reactive species levels in cells and animal models, demonstrating a physiological molecular relationship between PON proteins and oxidative stress. [6] revealed that PON2 lowers ubisemiquinone-mediated mitochondrial superoxide production and apoptosis independent of its lactonase activity, based on the observation that PON2 is present in subcellular mitochondrial fractions [17]. On other side, GSH may also bind to anticancer medications, which can then be euxed out of the cell by various resistance-associated protein transporters, which are the primary causes of treatment resistance in several malignancies [14]. All of the documented above demonstrate how Sorafenib effects on hepatic injury induced by CCl_4 in male of rats. The results of the investigation revealed that all livers in the control group had normal parenchyma at the end of the trial, while all livers in the CCl4 group had abnormal parenchyma. A histological imaging revealed that the livers of the rats that were given pistacia Khinjuk or/and Sorafenib drug differed considerably from those who were given CCl_4. These findings are in accordance with a previous study that found that the presence of phenolic compounds in the rat liver reduced the degree of acrylamide-induced DNA damage [20]. The study's findings reveal that pre-treatment with alcoholic extract provides considerable protection against toxin "CCl4" damage, suggesting that the plant's defensive components are only present in ethanolic extracts. These actions might be mediated by chemical components acting through the hepatic MDME inhibitory pathway and/or the presence of anti-oxidants in plant constituents.

5. Conclusion

The administration of *pistacia Khinjuk* appears to contribute to its protective effect against CCl4-induced hepatic injuries through the maintains the oxidative stress. As a result, oral *pistacia Khinjuk* ingestion as an adjuvant natural treatment for subjects may be recommended in the future to guard against the inhibitory effects of liver failure.

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