Protective Effects of Tribulus terrestris Extract on Hepatotoxicity Induced by Cytarabine (Ara C) Chemotherapy in Male Rats

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***Abstract*— Hepatotoxicity is a common clinical manifestation associated with a wide range of anticancer therapies. Because of the inherent toxicity of anticancer therapies, oncologists must maintain a broad understanding of their effects on the body, including the liver. Therefore, the study was conducted to examine the effects T. terrestris extract on damaged liver as a result of giving cytarabine. In the experiment, twenty-four male rats were employed. The rats divided to four group each group with six rats, lasted about during 28 days the rats were administration as the following groups, which include: group (G1) control negative: control negative: six rats were administered with normal saline, and were euthanized after four weeks, group (G2) of cytarabine (Ara-C 25): in this group six rats will be administrating by cytarabine (Ara-C 25 mg/kg bw) intraperitoneally every day for four weeks is the control positive: in this group six rats will be administered by T. terrestris extract (250 mg/kg body weight) orally for four weeks, group (G3) experimental group: in this group six rats will be administrating by cytarabine (Ara-C 25 mg/kg bw) intraperitoneally + T. terrestris extract (250 mg/kg bw) orally for four weeks, group (G4) is the control positive: in this group six rats will be administered by T. terrestris extract (250 mg/kg body weight) orally for four weeks. The purpose of this study was to evaluate the protective role T. terrestris extract on cytarabine induced hepatotoxicity on liver male rats.**

***Keywords* — Hepatotoxicity, T. terrestris extract, Cytarabine (Ara-C), Antioxidant.**

I. INTRODUCTION

THE performs various metabolic tasks and is a critical organ in the food and drugs biotransformation. Hepatic disorders are a primary global health concern. Because of its remarkable potential for regeneration, toxic substances are the primary cause of hepatic diseases. Drug toxicity, xenobiotic toxicity, and oxidative stress all have a significant impact on the liver. The liver is a primary carcinogen target due to its active proliferative response. Since it is crucial for metabolizing many medications and poisons, including cytotoxic chemotherapy regimens, it is particularly vulnerable to harm [1].

The liver is known only in vertebrates. It is a critical organ due to its numerous essential biological activities, such as removing toxins, producing important and necessary compounds for food digestion, and growing the organism [2].

Xenobiotic compounds can cause severe damage to the body. The liver can protect against damage, so it is considered an essential organ in metabolizing substances. Bio activation of some compounds in the liver can be associated with liver damage of course, the features of restoration and regeneration power have made it considered a powerful organ. In case of lack of regeneration or high severity of liver damage, the person will suffer liver failure or death. An increase in the arbitrary use of some drugs, either orally or by prescription, or more interest in the excessive use of dietary supplements or dietary drugs, or the use of xenobiotic chemical compounds can provide the basis for further damage to the liver [3].

II. MATERIALS AND METHODS

A. Experimental Animals

Twenty-four albino rats with Wight ranging 280-300 g were prepared from the College of Veterinary Medicine University of Kerbala laboratory, kept in plastic cages with diameters of 50×35×15 cm and under appropriate laboratory conditions (25-28 C°, 40٪ - 60٪humidity, and ventilation and the light system was 12 hours per day. Each cage consists of not more than four rats. Male rats were fed on the standard chow and drinking water ad libitum throughout the experiment. To acclimatize, they were kept fifteen days before the experimental assay.

B. Experiment Design

A total of 24 male rats were classified into 4 groups (6 rats in each group):

1- Group (G1) control negative: control negative: Six rats were administered with normal saline, and were euthanized after four weeks.

2- Group (G2) of Cytarabine (Ara-C 25): in this group six rats will be administrating by Cytarabine (Ara-C 25 mg/kg bw) intraperitoneally every day for four weeks [4].

3-Group (G3) experimental group: in this group six rats will be administrating by Cytarabine (Ara-C 25 mg/kg bw) intraperitoneally + T. terrestris extract (250 mg/kg bw) orally

for four weeks (5).

4- Group (G4) is the control positive: in this group six rats will be administered by T. terrestris extract (250 mg/kg body weight) orally for four weeks [5].

Serum Collection

Blood sample collection was performed after 28 days of experimental assays with a heart puncher, and the rat was anesthetized with chloroform shown in (figure 2-1). Blood was collected in a unique gel tube without anticoagulant and allowed to clot, and the tubes were centrifuged for 10 minutes/ 3000 RPM to collect serum. Serum was collected and kept at -20oC till further assays.

III. Results

A. Measuring the level of liver enzymes

Comparison of serum Angiotensin Converting Enzyme (ACE) in the experimental groups

The current study shows that the amount of Angiotensin converting enzyme (ACE) in cytarabine group (G2) did not show any significant difference with control group ($p > 0.05$) (figure 1). But there is a significant decrease in serum ACE in G3 ($p<0.05$) and G4 ($p<0.01$) groups as compared with cytarabine group. While there is no significant difference between control group (G1), Cytarabine and T. terrestris extract group (G3) and T. terrestris group (G4) ($p>0.05$). The main value of ACE for all groups is shown in table 1.

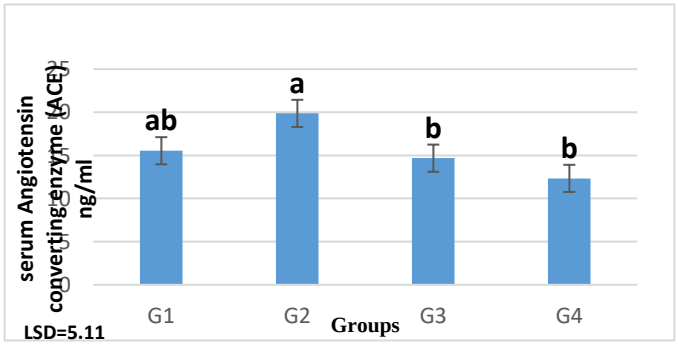

Figure 1: Comparison of serum Angiotensin Converting Enzyme in the experimental groups.

Table 1: Comparison of liver enzymes in the experimental groups.

Pa. \ Gr.	G1	G2	G3	G4	P-value
ACE (ng/ml)	15.53± 2.17^{ab}	19.86± 1.74 ^{a}	14.675± 1.49 ^{b}	12.3±1 .41 ^{b}	0.041
GGT (IU/L)	15.86 ±1.49 ^{ab}	21.74 ±1.57 ^{a}	16.3 ±3.76 ^{ab}	10.48 ±1.22 ^{b}	0.019
AST (U/A)	26.909 ±1.79 ^{b}	40.57 ± 3.51 ^{a}	24.8916 ±5.1 ^{b}	23.16 ±3.39 ^{b}	0.012
ALT (U/A)	24.90 ±1.16 ^{b}	29.78 ±1.77 ^{a}	24.89±1 .66 ^{b}	23.18 ±1.45 ^{b}	0.035

The results represented as mean ± SE.
Different capital letters denote a significant difference ($P>0.05$) between groups.
Similar capital letters denote the absence of significant differences ($P>0.05$) between periods.
G 1: Rats were administered with normal saline (1ml/kg), for four weeks.
G 2: Rats were administrating by Cytarabine (25 mg/kg) intraperitoneally every day for four weeks.
G 3: Rats were administrating by Cytarabine (25 mg/kg) intraperitoneally and T. terrestris extract (250 mg/kg) orally for four weeks.
G 4: Rats were administered by T. terrestris extract (250 mg/kg) orally for four weeks.

Comparison of serum Gama glutamyl transferase (GGT) in the experimental groups

The current study shows that the amount of Gama glutamyl transferase (GGT) in cytarabine group (G2) did not show any significant difference with control group ($p>0.05$) (figure 2). Also, this study shows that the amount of ACE in G3 group nonsignificant decreased in comparison with cytarabine group and reached to the control group. There is a significantly decrease ($p<0.01$) in amount of GGT in T. terrestris group (G4) as compared with cytarabine group. While there is no significant difference between control group (G1), Cytarabine and T. terrestris extract group (G3) and T. terrestris group (G4) ($p>0.05$). The main value of GGT for all groups is shown in table 1.

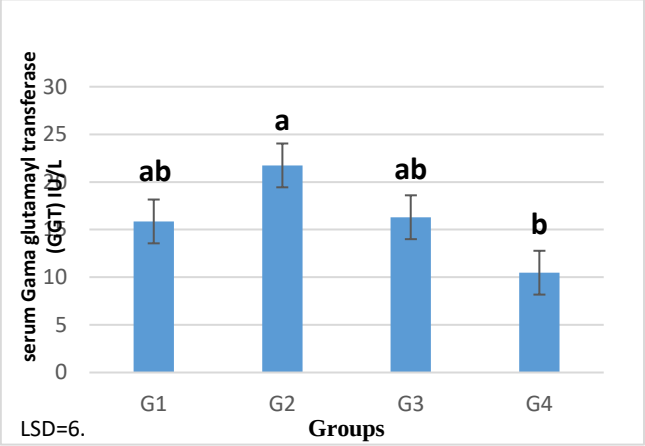

Figure 2: Comparison of serum Gama glutamyl transferase in the experimental groups.

Comparison of serum Aspartate aminotransferase (AST) in the experimental groups

The current study shows that there is a significant increase ($p<0.01$) in serum Aspartate aminotransferase (AST) in cytarabine group (G2) as compared with other groups (figure 3). Also, this study shows that the amount of AST in G3 group significantly decreased in comparison with cytarabine group and reached to the control group. There is no significant difference between control group (G1) and T. terrestris group (G4) ($p>0.05$). The main value of AST for all groups is shown in table 1.

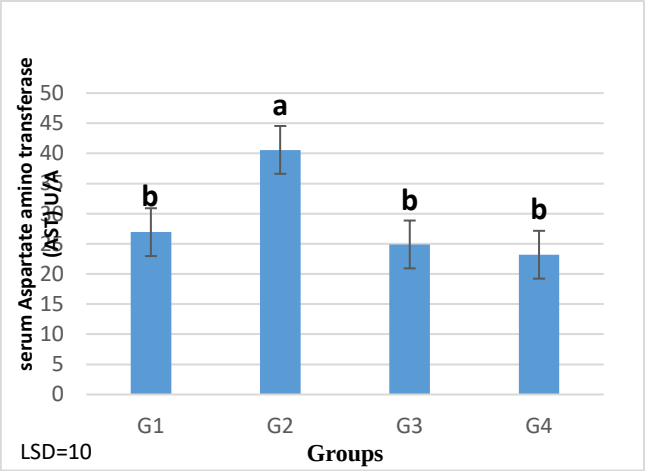

Figure 3: Comparison of serum Aspartate aminotransferase in the experimental groups.

Comparison of serum Alanine aminotransferase (ALT) in the experimental groups

The current study shows that there is a significant increase ($p<0.05$) in serum Alanine aminotransferase (ALT) in cytarabine group (G2) as compared with other groups (figure 4). Also, this study shows that the amount of ALT in G3 group significantly decreased in comparison with cytarabine group and reached to the control group. There is no significant difference between control group (G1) and T. terrestris group (G4) ($p>0.05$). The main value of ALT for all groups is shown in table 1.

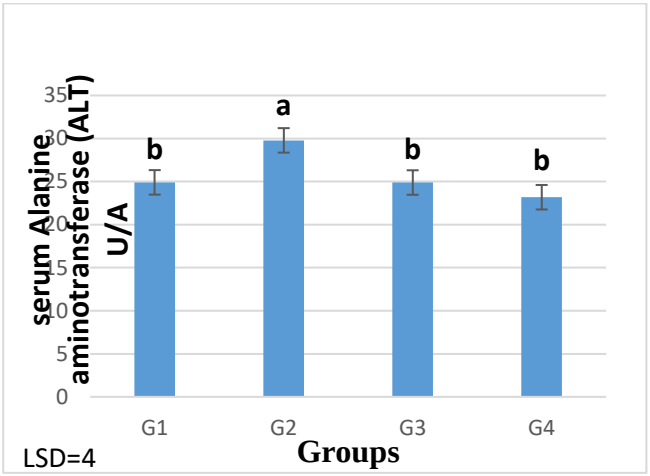

Figure4: Comparison of serum Alanine aminotransferase in the experimental groups.

Investigating the antioxidant level of blood serum in experimental groups

Comparison of serum superoxide dismutase enzyme (SOD) levels in experimental groups

The current study shows that the amount of serum Superoxide dismutase (SOD) in cytarabine group (G2) did not show any significant difference with control group ($p>0.05$) (figure 5). But there is a significant increase in serum SOD in G3 ($p<0.05$) and G4 ($p<0.01$) groups as compared with cytarabine group. While there is no significant difference between control group (G1), Cytarabine and T. terrestris extract group (G3) and T. terrestris group (G4) ($p>0.05$). The main value of SOD is shown in table 2.

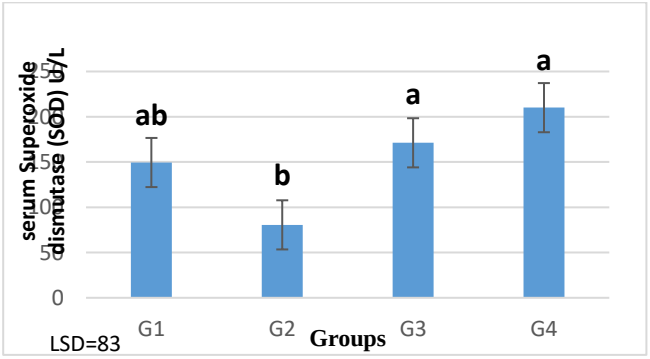

Figure 5: Comparison of serum superoxide dismutase (SOD)in the experimental groups.

Table 2: Comparison of serum superoxide dismutase enzyme (SOD), catalase enzyme (CAT) and malondialdehyde (MDA) levels in experimental groups.

Gr. / Par.	G1	G2	G3	G4	P-value
SOD (U/L)	149.45 ±23.69 ab	80.58 ± 20.72 b	171.21± 39.89 a	210.03 ±25.2 a	0.030
CAT (KU/L)	0.980 ±0.02 a	0.784 ±0.06 b	0.880 ±0.06 ab	0.987 ± 0.05 a	0.049
MDA (µm/L)	1.917 ±0.27 b	3.325 ±0.15 a	2.679±0.43 ab	1.948 ±0.23 b	0.008

The results represented as mean ± SE.
Different capital letters denote a significant difference (P>0.05) between groups.
Similar capital letters denote the absence of significant differences (P>0.05) between periods.
G 1: Rats were administered with normal saline (1ml/kg), for four weeks.
G 2: Rats were administrating by Cytarabine (25 mg/kg) intraperitoneally every day for four weeks.
G 3: Rats were administrating by Cytarabine (25 mg/kg) intraperitoneally and T. terrestris extract (250 mg/kg) orally for four weeks.
G 4: Rats were administered by T. terrestris extract (250 mg/kg) orally for four weeks.

Comparison of serum catalase enzyme (CAT) levels in experimental groups

The current study shows that there is a significant ($p<0.05$) decrease in serum catalase (CAT) in cytarabine group (G2) as compared with control group (G1) (figure 6). Also, this study shows that the amount of CAT in G3 group significantly increased in comparison with cytarabine group and reached to the control group. There is no significant difference between control group (G1) and T. terrestris group (G4) ($p>0.05$). The main value of CAT is shown in table 2.

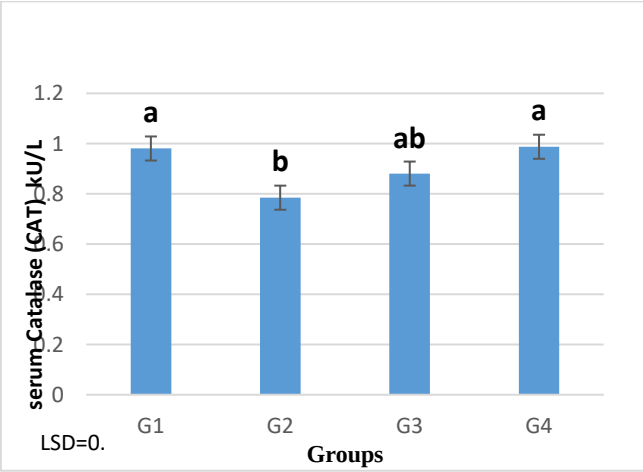

Figure 6: Comparison of serum catalase (CAT) in the experimental groups.

Comparison of serum malondialdehyde (MDA) levels in experimental groups

The current study shows that there is a significant ($p<0.01$) increase in serum malondialdehyde (MDA) in cytarabine group (G2) as compared with the other groups (G1, G2, and G4). In combination group (G3) the level of malondialdehyde significant ($p<0.01$) decreased as compared with cytarabine group. On the other hand, control group (G1) and T. terrestris group (G4) show no significant difference between them ($p>0.05$) (figure 7). The main value of MDA is shown in table 2.

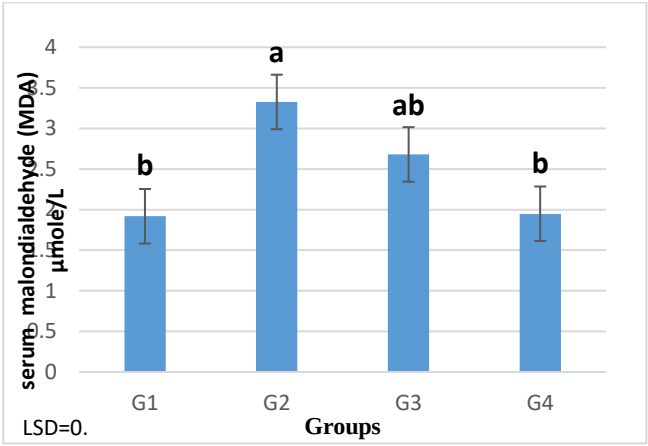

Figure 7: The level of malondialdehyde (MDA) in the experimental groups

IV. Discussion

Effect of cytarabine and in combination with T. terrestris extract on the liver enzymes in adult male rats

This study shows a significant increase in serum Angiotensin converting enzyme (ACE) in cytarabine group (G2) compared with cytarabine + T. terrestris extract group (G3) and T. terrestris group (G4). while there is no significant difference between control group (G1) with other groups.

This result is consistent with [6] [7].

ACE is an essential enzyme in regulating blood pressure and fluid balance. This enzyme changes angiotensin I to angiotensin II, a dominant vasoconstrictor that narrows blood vessels and raises blood pressure [8]. But some drugs, such as ACE inhibitors, prevent the activity of ACE. Elevated levels of ACE in the blood can be a sign of several different conditions, such as Hodgkin's lymphoma. The liver controls the renin-angiotensin-aldosterone system (RAAS), a complex system that regulates blood pressure, electrolyte balance, and fluid homeostasis in the body. Any damage in the liver will lead to an increase in ACE [9].

T.terrestris may have an inhibitory effect on ACE, potentially leading to a decrease in blood pressure. T.terrestris may have the potential as an anti-hypertensive agent. T.terrestris has also been demonstrated to have antioxidant, anti-inflammatory, and immune-modulating characteristics, which may give to its health advantages [10].

Gamma-glutamyltranspeptidase is primarily found in liver cells. GGT has been identified as a clinical marker for free radical formation and proinflammation. GGT-related

pathomechanism is that GGT increases cysteine availability to promote intracellular glutathione, the primary thiol antioxidant in humans, and resynthesis, thereby mitigating oxidant stress.

According to the current study, there is a substantial increase in serum Gamma-glutamyl transpeptidase (GGT) in the cytarabine group (G2) as compared to the other groups. This data agreement with [6] [7] who, found the liver enzymes (ALT, AST, and GGT) were elevated. Several factors influence serum GGT levels, including alcohol consumption, body fat content, plasma lipid/lipoprotein and glucose levels, and many different drugs.

Certainly, elevations of serum GGT belong on the list of biomarkers linked to the metabolic syndrome [8].

The current study shows that there is a significant increase in serum Aspartate aminotransferase (AST) in cytarabine group (G2) as compared with other groups. Also, this study shows that the amount of AST in G3 group significantly decreased in comparison with cytarabine group and reached to the control group. There is no significant difference between control group (G1) and T. terrestris group (G4).

In present study shows that there is a significant increase in serum Alanine aminotransferase (ALT) in cytarabine group (G2) as compared with other groups. Also, this study shows that the amount of ALT in G3 group significantly decreased in comparison with cytarabine group and reached to the control group. There is no significant difference between control group (G1) and T. terrestris group (G4).

ALT and AST are enzymes commonly found within liver cells and involved in various metabolic processes. When liver cells are damaged or destroyed, these enzymes leak into the bloodstream, causing an increase in their levels. Elevations in ALT and AST are typically seen in conditions of liver injury [9] [10].

Cytarabine is a chemotherapy medication commonly used to therapy of diverse cancer, such as leukemia and lymphoma. It prevents DNA replication in cancer cells, which can lead to cell death. However, cytarabine can also affect normal cells, including liver cells, and may cause liver toxicity [11].

Cytarabine can generate reactive oxygen species (ROS) in liver cells, resulting in to oxidative stress and injury to cellular components, including liver enzymes [12].

T.terrestris may also help protect the liver by raising the production of certain enzymes include in detoxifying deleterious materials in the liver.

Also, T. terrestris may protect the liver by reducing inflammation. Inflammation is a typical response to liver damage, and chronic inflammation can lead to further liver damage and the development of liver disease. Studies have shown that T. terrestris contains compounds such as saponins and terpenoids that have anti-inflammatory properties and may help reduce inflammation in the liver [13].

Different anticancer therapy might injure the liver because the liver detoxifies the toxic compounds, metabolizes the drug, and excretes waste products. Chemotherapy is associated with some side effects, such as hepatitis. The hepatotoxic effect depends on the concentration of the hepatotoxicants, which could include either the parent toxic substance or the toxic metabolite, this showed through the elevation of liver enzymes concentration in the blood. Cytarabine is currently the main drug used to treat anti-cancer patients. However, due to side effect to ara-C, a new combination is needed to improve treatment outcome. As is known to all, T.terrestris is a traditional herb which also has anti-cancer activity in some cancer cells. In our previous study, we found that, T.terrestris help protect the liver by increasing the production of certain enzymes involved in detoxifying harmful substances in the liver.

Effect cytarabine and in combination with T. terrestris extract on serum anti-oxidant in adult male rats

This research shows a significant decreas in serum superoxide dismutase (SOD) & catalase (CAT) in the cytarabine group compared with cytarabine + T. terrestris extract group (G3) and T. terrestris group (G4). However, there is a significant increase in the serum malondialdehyde (MDA) level in the cytarabine group as compared to another group.

This result is in agreement with [17]. SOD and catalase are enzymes that play an essential role in protecting cells from oxidative stress. It happens when there is no equilibrium between the ROS synthesizing and the cell's ability to counteract them with antioxidants. Damage in the cellular components, including DNA, proteins, and lipids, and developing cancer or other diseases might have resulted from the ROS effect [14].

Several studies have reported that cytarabine can decrease the levels of SOD and catalase in various tissues, including the liver, that cytarabine treatment decreased SOD and catalase levels in the liver of rats, leading to an increase in oxidative stress and liver damage, cytarabine and its metabolites may interfere with the expression or activity of these enzymes, leading to a decrease in their levels. Additionally, cytarabine may generate ROS directly, which can overwhelm the cells' antioxidant defenses and diminish SOD and catalase levels [15]. A diminish in SOD and catalase levels is a common side effect of cytarabine. It is usually reversible and does not necessarily indicate permanent damage. However, a prolonged decrease in these antioxidant enzymes may be related to the development of oxidative stress and cell damage, which may have long-term consequences [16].

Investigating the effects of cytarabine on SOD2 gene expression in hepatic cells [17] found that cytarabine treatment decreased the expression of the SOD2 gene and suggested that a decrease in the production of SOD may contribute to the development of oxidative stress in liver cells.

Also, other another study found that cytarabine treatment decreased the expression of the CAT gene and suggested that this decrease may contribute to oxidative stress in liver cells, this study found that cytarabine treatment decreased the expression of the CAT gene, leading to a decrease in CAT enzyme activity and prolonged decrease in CAT levels and activity may contribute to the development of oxidative stress and cell damage, which may have long-term consequences [18].

Cytarabine has been shown to increase malondialdehyde (MDA) levels, a biomarker of lipid peroxidation and oxidative stress. Several studies have investigated the effects of cytarabine on MDA levels in various tissues, including the liver [19].

Sillar et al. [20] believed that cytarabine and its metabolites might generate ROS directly, which can cause lipid

peroxidation and the formation of MDA. Additionally, cytarabine may interfere with antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), leading to an imbalance between ROS production and antioxidant defense and promoting lipid peroxidation.

Several studies have investigated the effects of T.terrestris on antioxidant enzymes, including SOD and catalase (CAT), which play a critical function in protecting cells from oxidative stress [21].

Tkachenko et al. (2020) demonstrated that the plant might contain bioactive compounds with antioxidant properties that stimulate the expression or activity of SOD and CAT enzymes.

T.terrestris extract increased the activity of the enzyme superoxide dismutase and catalase, which protect liver cells from damage [22].

Additionally, T.terrestris may increase the availability of essential micronutrients such as zinc and selenium, which are important cofactors for SOD and CAT activity.

One of the primary bioactive compounds found in T.terrestris is saponins. These compounds have been shown to have diverse biological actions, including antioxidant and anti-inflammatory results [23]. Another bioactive compound found in T.terrestris is protodioscin. This compound has been shown to have antioxidant effects and to protect against oxidative damage in animal models. Additionally, protodioscin has been shown to improve the liver's activity of antioxidant enzymes such as SOD and CAT [24]. T.terrestris also contains various flavonoids, which are known for their antioxidant properties [25]. These compounds have been shown to scavenge free radicals and diminish oxidative stress in vitro and animal models.

Considering the pharmacological mechanism of Cytarabine, we analyzed liver's activity of antioxidant enzymes such as SOD and CAT. To further investigate the reason why combine T.terrestris with ara-C to improve the liver's activity of antioxidant, we found Cytarabine elevated cytotoxicity likely by increasing the malondialdehyde (MDA) levels. One possible way in which T.terrestris may protect the liver is through its antioxidant properties. When there is no equilibrium between producing the ROS and removing them, and the synthesized ROS is more than the ability of the body to eliminate, the liver organ would be very susceptible to oxidative stress-induced injuries by Cytarabine. In our results evaluated the effects of that T.terrestris contains compounds such as flavonoids and phenolic acids that have antioxidant activity and may help protect liver cells from oxidative damage.

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