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Protective effects of wheat and barley grasses on hepatotoxicity induced by tramadol in male rats

Lamiaa M. Abd EL-Maoula*
Nutrition and Food Science Department, Faculty of Home Economics, Al- Azhar University, Tanta, Egypt
* dr_lamiaamostafa@azhar.edu.eg

ABSTRACT

Nowadays tramadol is becoming abused more popular among teens in most countries worldwide; especially between males. The aim of the present study was to investigate the protective effects of barley and wheat grasses on hepatotoxicity induced by tramadol in male rats. Thirty male albino rats weighing (150-200 g) were divided into two main groups: The first group (5 rats) was fed on basal diet and kept as a negative group (G-). The second group (25rats) was fed on basal diet and administrated tramadol (30mg/kg/day) orally for 30 days. After that, the rats were divided into five subgroups as following: Subgroup (1): kept as a positive group (G+). Subgroups (2&3) were given tramadol +wheat grass (250 and 500mg/kg body weight) and Subgroups (4&5) were given tramadol + barley grass (250 and 500mg/kg body weight) orally for 30 days. The biochemical data showed elevated liver enzymes; alanine transaminase (ALT), aspartate transaminase (AST), Alkaline Phosphatase (ALP), total bilirubin, direct bilirubin and in direct bilirubin as well as liver weight in tramadol group (G+). A significant increase in malondialdehyde (MDA) and nitric oxides (NO) were also noticed in (G+). While, there were a significant decrease in glutathione peroxidase (GPx), reduced glutathione (GSH) and catalase (CAT) levels in tramadol group (G+). Concomitant use of barley and wheat grass with tramadol induced improvement in the hepatotoxic effects. The best results were recorded for the groups treated with high dose (500mg/kg body weight) of barley and wheat grass. It was concluded from the present results that administration of barley and wheat grass with tramadol can ameliorating tramadol-induced hepatotoxicity which might be due to its antioxidant potential.

Keywords: Hepatotoxicity, tramadol, liver enzymes, antioxidant enzymes, barley grass, wheat grass.

INTRODUCTION

Tramadol is a synthetic opioid analgesic that acts centrally and is used to treat moderate to severe pain (Pinho *et al*., 2013). Tramadol works as an analgesic by limiting serotonin and norepinephrine reuptake as well as binding to μ -opioid receptors (Grond and Sablotzki, 2004). Tramadol usage can lead to serotonin syndrome (SS), a severe illness characterised by altered mental status, agitation, tremors, dilated eye pupils, and enhanced reflexes caused by excessive serotonergic activity (Takeshita and Litzinger, 2009). Tramadol is primarily metabolised in the liver by the enzymes cytochrome P450, cytochrome P4503A, and cytochrome P450 isozyme, where it is O- and N-demethylated to five various metabolites then being conjugated with glucuronic acid and sulphate (Raffa, 2008). O-desmethyl tramadol is the most active metabolite with more potent pharmacological activity when compared to the parent tramadol substance (Barbosa *et al*., 2016). Tramadol is metabolized in the

liver and then eliminated mostly by the kidneys; as a result, these organs are regarded to be the primary target organs for tramadol poisoning (Barbosa *et al*., 2017). The hazardous effects of tramadol should be considered during long-term treatment, especially at high doses (Watson *et al.*, 2004). Due to the sheer widespread usage of tramadol, hepatotoxicity is a clinical and economic concern (Janssen-Ortho, 2005).

Ninety percent of the population is affected by oxidative stress, which manifests itself in the form of arthritis, ischemia, neurodegeneration, and chronic liver disease.

In the last few years, tramadol consumption has become more common in Egypt and other Middle Eastern countries. This could be due to its low cost and widespread availability (Fawzi, 2011).

For thousands of years, cereal grass has been used to treat a variety of diseases. In the last ten years, human intake of wheat grass and other cereal grasses has expanded considerably (Jain and Argal, 2014). Wheat grass (*Triticum aestivum*) contains a lot of vitamins, minerals, amino acids, chlorophyll and enzymes. Fresh juice has been demonstrated to have anti-inflammatory, anti-ulcer, antioxidant, anti-cancer, and anti-arthritic properties. Wheat grass is said to aid blood flow, digestion, and general detoxifying of the body so it contains physiologically active chemicals and minerals, as well as antioxidants (Chauhan, 2014). Wheat grass is used in herbal system of medicine and described as antioxidant, immunomodulatory, ant-ibacterial, astringent, diuretic, laxative, colitis, acidity and kidney malfunction (Ashok, 2011). Wheat grass offers a number of health-promoting properties. It is well-known for its therapeutic properties. It is used as a purifying and cleansing agent, and due of its nutritional value, it can also be called a body builder (Shaikh and Majaz, 2016). Wheat grass is a primary source of several nutrients, including bioflavonoids, chlorophyll, phenol compounds, iron, magnesium, calcium, amino acids and vitamins A, B, C, and E, all of which play a role in disease prevention (Durairaj *et al*., 2014). At the same time, Wheat grass contains anti-cancer compounds such as laetrile and selenium, as well as cytochrome oxidase, superoxide dismutase (SOD) and mucopolysaccharide (Wheat and Currie, 2008).

Barley (*Hordeum vulgare* L.) is the world's fourth most significant cereal crop and contains the highest amount of dietary fiber; its malt is used in functional foods. Based on phytochemicals such as flavonoids, β-glucan, tocols, lignans, phytosterols, phenolic acids, and folate, regular consumption of whole grain barley and its hydroalcoholic extract lowers the risk of chronic diseases (cancer, obesity, cardiovascular disease, diabetes, and etc.) (Idehen *et al*., 2017).

Lee *et al.* (2016) indicated that *Hordeum vulgare* L. is the source of antioxidants and naturally beneficial substances in its bran, leaves, seeds and sprouts. Consumption of barley, which includes many medicinally active phytocompounds and a wide range of vitamins, eight essential amino acids and minerals, is usually connected with improved health (Lahouar *et al*., 2015). Barley grass, which is the young leaves of barley picked about 10 days after sowing the seeds, has gotten a lot of attention recently as a functional food. The highest nutrient concentrations are found in the green mass during a brief time of vegetation, and the nutritional profiles of green cereal plants alter rapidly as they expand (Ehrenbergerová *et al*., 2007). It has also been observed that barley young leaves have antihypertensive, depressive, antidiabetic, and cancer-prevention capabilities, as well as reducing

inflammation and pain by functioning as a free radical scavenger (Seo *et al*., 2013).

The purpose of this research was to investigate the potential protective effects of wheat and barley grasses due to their biologically active compounds and antioxidant abilities against tramadol induced hepatotoxicity in male rats.

MATERIALS AND METHODS

Materials:

1- Barley grass and wheat grass weren obtained from Sakha Research Center (Kafr Elsheikh, Egypt).
2- Tramadol tablets, each contains 225 mg tramadol hydrochloride were obtained from October Pharma Company (Giza, Egypt).
3- Thirty normal male albino rats of Sprague Dawley Strain weighing (150 to 200 gm.) were obtained from the experimental animal house in Food Technology Research Institute, Agric. Res. Center, Giza, Egypt.

Methods:

Preparation of Wheat and Barely grass powder:

Wheat and barley grains were first cleaned and eliminated from dust, broken particles, and other foreign materials and then soaked overnight in water to be cultivated in a container. The soaked seeds were individually spread on wet jute bags, covered by muslin cloth and one more wet jute bag. Then, the seeds were sprinkled by water every 12 hr. till finishing the germination period. After the ninth day grasses were harvested and chopped with knife. It was dried in shade and powdered with a mechanical grinder. The powder was passed through sieve no.40 and stored in a labeled airtight container for study (Jain and Argal, 2014).

Experimental Design

Thirty healthy adult male albino rats "Sprague Dawley strain" weighing (150 to 200 g) were kept in single wire cages with wire bottoms under hygienic conditions. Rats were divided into two main groups:

The first group (5 rats) was fed on basal diet and administrated distilled water orally for 30 days and kept as a negative control group **(G-).**

The second group (25 rats): was fed on basal diet and administrated orally tramadol at dose (30 mg/kg/day), for 30 days to induce hepatotoxicity. This dose is 1/10 of LD50. LD50 is 286–300mg/kg **(El-khateeb *et al*., 2015).** After that, these rats were divided into five subgroups (each consisted of 5 rats) as follows:

Subgroup (1): rats were orally administrated tramadol (30mg/kg/day) for 30 days and Kept as a positive control group **(G+).**

Subgroup (2): rats were orally administrated tramadol (30mg/kg/day) + barley grass (250mg/kg/day).

Subgroup (3): rats were orally administrated tramadol (30mg/kg/day) + barley grass (500mg/kg/day).

Subgroup (4): rats were administrated tramadol (30mg/kg/day) + wheat grass (250mg/kg/day).

Subgroup (5): rats were administrated tramadol (30mg/kg/day) + barley grass (500mg/kg/day).

Rats received orally wheat and barley grasses for 30 days at doses (250 or 500 mg/kg/day). These doses were freshly prepared, suspended in distilled water before taken orally (Abed *et al.*, 2017).

Biological evaluation:

At the end of the experiment, feed intake, body weight gain, liver weight as a percent of total body weight were determined according to Chapman *et al*. (1959), as follow:

Feed intake = Initial diet weight (g) – left over diet weight (g),
Body weight gain percent (BWG %) = {(Final body weight – Initial body weight)/Initial body weight} x 100,
Relative liver weight = (liver weight/ Final body weight)× 100.

The feed efficiency ratio was calculated according to Hosoya (1980) as follow:
FER=Body weight gain (g) /total feed intake (g).

Liver was removed from each rat, carefully washed with saline solution, dried with filter paper and weighted based on Drury and Wallington (1980).

Biochemical analysis:

Determination of the activity of liver enzymes:

Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were determined in the serum according to Reitman and Frankel (1957). Alkaline phosphatase (ALP) determination was performed according to Roy (1970).

Determination of serum Bilirubin:

The total bilirubin was determined in serum according to Doumas *et al*. (1973). Direct Bilirubin was determined in serum according to Chary and Sharm (2004). Serum Indirect Bilirubin was calculated according to Chary and Sharm (2004) equation:
Indirect Bilirubin (g/dL)=Total Bilirubin (g/dL)-Direct Bilirubin (g/dL).

Determination of serum proteins:

The total protein (T.P) was determined according to Sonnenwirth and Jaret (1980). Albumin was determined according to the method of Drupt (1974) as modified by, Spencer and Price (1977). Globulin was calculated according to Chary and Sharm (2004) equation:
Serum globulin (g/dL) = total protein (g/dL)-Albumin (g/dL).

Antioxidant enzymes in serum

Glutathione peroxidase (GPx), Catalase (CAT), Nitric oxide (No) and Malondialdehyde (MDA) were determined in serum according to Moshage *et al*.(1995) and Ahmadvand *et al*. (2014).

Antioxidant enzymes in liver tissue

Catalase (CAT), reduced glutathione (GSH), Malondialdehyde (MDA) and Nitric oxide (No) were determined in liver tissue according to Green *et al*. (1982) and Aebi (1974).

Statistical analysis

Data were represented as means ± standard deviation (SD). Differences were statistically analyzed by one-way analysis of variance (ANOVA test) using SPSS 16 software package and considered significant at P values < 0.05 Armitage and Berry (1987).

RESULTS

Biological evaluation

Data listed in Table (1) showed the effect of wheat and barley grasses powder on feed intake (FI), body weight gain (BWG) %, feed efficiency ratio (FER) and relative liver weight. All experimental groups treated with wheat and barley grasses powder recorded significant increase in FI and FER when compared to (+ ve) control group (17.13±0.56 & 0.05±0.02, respectively). On the other hand, the results of FI recorded non-significant differences between all treated groups and normal control group (G-). As for BWG %, it could be observed that all experimental groups treated with wheat grass (250 & 500 mg/kg) and barley grass (500 mg/kg) had significant increase compared to tramadol group. The best results for BWG were recorded for the groups treated with wheat and grasses powder (500mg/kg). While

group treated with wheat grass (250mg/Kg) recorded the best result for FER.

Table (1) also, illustrate the change in relative liver weight % for controls and treated groups. Results of relative liver weight (%) showed that all treated groups had significant decrease in mean values when compared with (+ve) control group (3.17±0.17).

Table (1). Effects of wheat and barley grasses powder on feed intake (FI), body weight gain (BWG), feed efficiency ratio (FER) and relative liver weight % in male rats.*

Groups	Parameters			
	FI (g)	BWG (%)	FER	Relative Liver weight %
Control –ve	18.9.± 0.23 [b]	30.71±4.02 [e]	0.16±0.02 [e]	2.06±0.16 [a]
Control +ve	17.13±0.56 [a]	22.00±3.68 [a]	0.05±0.02 [a]	3.17±0.17 [b]
Tramadol + wheat grass (250mg/Kg)	19.26±0.15[b]	24.38±4.53[b]	0.12±0.02 [d]	2.06±0.20[a]
Tramadol + wheat grass (500mg/kg)	19.22± 0.25[b]	28.21±5.98[de]	0.09±0.02[c]	2.16±0.10[a]
Tramadol + barley grass (250mg/kg)	18.9±0.19[b]	22.57±1.23[a]	0.08±0.01[c]	2.08±0.40[a]
Tramadol + barley grass (500mg/kg)	19.02± 0.24[b]	25.43±2.20[c]	0.07±0.01 [b]	2.37±0.19[a]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at p≤0.05.

Liver function

Data presented in Table (2) declared that all treated groups showed a significant reduction in ALT, AST and ALP (U/L) as compared to the positive control group. The best results for ALT were recorded for the groups treated with wheat or barley grasses (500mg/kg). While those treated with wheat grass (500mg/kg) recorded the best result for AST and ALP (99.63±1.56 & 123.43±2.31, respectively).

Table (2). Effects of wheat and barley grasses powder on liver enzymes (ALT, AST & ALP) in male rats.*

Groups	Parameters		
	ALT(U/L)	AST(U/L)	ALP(U/L)
Control –ve	48.36±1.83[a]	93.80±1.26[a]	117.20±2.36[a]
Control +ve	145.20±1.93[d]	277.87±3.19[f]	263.20±2.23[e]
Tramadol + barley grass (250mg/kg)	64.63±2.90[c]	124.40±3.62[e]	137.60±2.11[d]
Tramadol + barley grass (500mg/kg)	54.27±1.57[b]	110.33±2.33[c]	132.83±2.35[c]
Tramadol + wheat grass (250mg/Kg)	61.77±2.02[c]	118.53±3.00[d]	131.45±2.73[c]
Tramadol + wheat grass (500mg/kg)	53.27±2.54[b]	99.63±1.56[b]	123.43±2.31[b]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at p≤0.05.

It was obvious that the mean values of T.B, D.B and ID.B (mg /dl) of (-ve) control group were lower than those of (+ve) control group, with significant difference between them. The treated groups showed a significant reduction in their mean values of T.B, D.B and ID.B (mg /dl) as compared to (+ve) control group. The best results for T.B and ID.B were recorded for the groups treated with dose (500mg/kg) of wheat or barley grasses. While the best results for D.B was recorded for the groups treated with wheat grass (500mg/kg), which

recorded the same value of D.B from those of normal control group (Table 3).

Table (3). Effects of wheat and barley grasses powder on total bilirubin, direct bilirubin and in direct bilirubin in male rats.*

Groups	Parameters		
	T.B (mg/dL)	D.B (mg/dL)	ID.B (mg/dL)
Control –ve	0.56±0.03[a]	0.14±0.01[a]	0.43±0.03[a]
Control +ve	1.10±0.05[e]	0.21±0.02[d]	0.89±0.04[e]
Tramadol + wheat grass (250mg/Kg)	0.78±0.03[c]	0.16±0.01[bc]	0.62±0.02[c]
Tramadol + wheat grass (500mg/kg)	0.68±0.03[b]	0.14±0.02[ab]	0.54±0.02[b]
Tramadol + barley grass (250mg/kg)	0.90±0.07[d]	0.18±0.01[c]	0.72±0.06[d]
Tramadol + barley grass (500mg/kg)	0.74±0.03[bc]	0.16±0.01[bc]	0.58±0.04[bc]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at p≤0.05.

Serum protein

Table (4) illustrates the change in the total protein, albumin and globulin (mg/dl) for controls and treated groups. Results of the total protein, albumin and globulin showed that (+ve) control group recorded mean value (3.79±0.06, 2.84±0.12 & 0.95±0.05, respectively) which are less than those of all the treated groups which had significant increase in this parameter. Numerically the best results for the total protein, albumin and globulin were recorded for the groups treated with wheat grass (500mg/kg), which recorded the nearest value of those of normal control group. Results of A/G ratio showed that all the treated groups had significant decrease in their mean values when compared with (+ve) control group (2.99±0.29).

Table (4). Effects of wheat and barley grasses powder on serum protein in male rats.*

Groups	Parameters			
	Total protein (g/dl)	Albumin (g/dl)	Globulin (dl g/)	A/ G Ratio
Control –ve	8.99±0.15[e]	5.07±0.06[e]	3.92±0.08[e]	1.30±0.01[a]
Control +ve	3.79±0.06[a]	2.84±0.12[a]	0.95±0.05[a]	2.99±0.29[b]
Tramadol + wheat grass (250mg/Kg)	7.3±0.02[c]	4.17±0.03[c]	3.13±0.04[bc]	1.33±0.03[a]
Tramadol + wheat grass (500mg/kg)	8.25±0.46[d]	4.68±0.28[d]	3.57±0.19[d]	1.31±0.01[a]
Tramadol + barley grass (250mg/kg)	6.73±0.37[b]	3.84±0.08[b]	2.88±0.34[b]	1.34±0.16[a]
Tramadol + barley grass (500mg/kg)	7.43±0.27[c]	4.21±0.12[c]	3.22±0.15[c]	1.31±0.03[a]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at p≤0.05.

Oxidative markers and antioxidants levels in serum

From Table (5) as a result of administration of tramadol 30 mg/kg/d, there were a marked reduction in the levels of some antioxidants in serum such as catalase (CAT) and glutathione peroxidase (GPX) as compared to (–ve) control

group. Also, there were significant increase for nitric oxides (NO) and Malondialdehyde (MDA) for tramadol group as compared to normal control. On the other hand, all experimental groups showed a significant reduction in NO and MDA and significant increase in GPX and CAT as compared to positive control group.

Table (5). Effects of wheat and barley grasses powder on antioxidant enzymes (NO, MDA, CAT and GPX) in serum of male rats.*

Groups	Parameters			
	NO (nmol/ml)	MDA (nmol/ml)	CAT (ng/ml)	GPX (ng/ml)
Control –ve	43.88±0.88 [a]	46.50±3.50 [a]	53.50±3.50 [d]	39.00±2.00 [d]
Control +ve	92.50±2.50 [e]	117.50±2.50 [e]	30.00±2.00 [a]	12.50±1.50 [a]
Tramadol + wheat grass (250mg/Kg)	76.50±6.50[d]	83.00±3.00 [d]	34.00±1.00[ab]	20.00±2.00[b]
Tramadol + wheat grass (500mg/kg)	61.25±0.75[c]	74.50±2.50[c]	43.50±1.50[c]	29.00±1.00[c]
Tramadol + barley grass (250mg/kg)	73.75±2.75 [d]	58.00±2.00 [b]	37.50±2.50[b]	22.50±2.50[b]
Tramadol + barley grass (500mg/kg)	51.25±1.25 [b]	48.50±1.50 [a]	52.00±3.00[d]	32.50±2.50[c]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at $p \leq 0.05$.

Oxidative markers and antioxidants levels in liver tissues

Table (6) shows that the mean values of NO and MDA in liver tissues had, high significant increase in positive control group (89.70±2.50 & 156.73±2.41) respectively) when compared to the normal rats (33.18±2.70 & 57.14±2.08, respectively). All treated groups showed significant decrease in NO and MDA as compared to tramadol group. While all experimental groups showed significant increase in CAT and GSH when compared with (+ve) control group. The best result for (NO, MDA, CAT and GSH) in liver tissues were recorded for the group treated with wheat grass (500mg/kg).

Table (6). Effects of wheat and barley grasses powder on antioxidant enzymes (NO, MDA, CAT and GSH) in liver tissues in rats.*

Groups	Parameters			
	NO (nmol/mg)	MDA (nmol/mg)	CAT (ng/mg)	GSH (ng/mg)
Control –ve	33.18±2.70[a]	57.14±2.08[a]	62.88±2.08[e]	9.44±0.51[f]
Control +ve	89.70±2.50[f]	156.73±2.41[e]	15.29±0.30[a]	1.70±0.17[a]
Tramadol + wheat grass (250mg/Kg)	52.43±2.85[c]	80.33±2.00[c]	40.03±1.85[c]	5.71±0.42[d]
Tramadol + wheat grass (500mg/kg)	41.96±1.48[b]	65.37±4.22[b]	54.14±1.83[d]	7.17±0.07[e]
Tramadol + barley grass (250mg/kg)	73.37±2.01[e]	108.44±3.00[d]	24.11±1.34[b]	3.76±0.12[b]
Tramadol + barley grass (500mg/kg)	59.51±1.78[d]	83.74±1.88[c]	37.44±1.96[c]	4.96±0.23[c]

*Data are presented as mean±SD. Values with different letters indicate significant differences among groups at $p \leq 0.05$.

DISCUSSION

Tramadol belong to the same family of codeine, morphine and oxycodone (Niesters *et al*., 2013). It is a powerful analgesic used to treat acute and chronic pain all over the world (Miotto *et al*., 2017). Its metabolism and excretion are controlled by the liver and kidney, in

addition to the high risk of tramadol addiction; it causes hepatotoxicity and nephrotoxicity (Janssen-Ortho, 2005).

Body and organ weights are important indices for drug toxicological evaluations because they might be influenced by drug-induced toxicity (Bailey *et al*., 2004). The present results demonstrated that tramadol induced decrease in body weight gain %, feed intake and feed efficiency ratio. The decrease occurred in the positive control group are attributed to tramadol abuse which led to some intestinal disturbances such vomiting, nausea and constipation with changing in appetite (Grond and Sablotzki, 2004). Oka *et al*. (2015) mentioned that administration of Tramadol inhibits the appetite centers in the hypothalamus, which could explain the tramadol group's decreased food consumption.

On the other hand, all rats given wheat and barley grasses, showed improvement in their body weight gain %, feed intake and feed efficiency ratio which confirm the ability of the examined samples to alleviate the toxicity of tramadol. Ikeguchi *et al.* (2014) cleared that adding barley leaf powder in the diet increased the fecal weight as it contains water-soluble dietary fibers and stimulating gastro-intestinal tract by lowering pH. Jorige and Akula (2015) reported that regular consumption of the wheat grass can develop the gastrointestinal system. Wheat grass juice reduces body weight as it contains selenium which improves function of the thyroid gland and contains potassium which aspects in coming off of water weight, so that, managing body weight. Also, wheat grass blocks the stomach, thus suppressing the appetite (Husain *et al.*, 2017).

Estimating relative organ weights is a crucial aspect of the toxicological evaluation of chemical compounds. In the present study there were no significant differences in relative liver weights between the tramadol and other groups. Lakshmi *et al*. (2015) reported that treatment with wheat grass extract before arsenic intoxication considerably reduced the body weight, kidney and liver weights of experimental rats following arsenic intoxication. Foda (2010) mentioned that adding young green barley leaves powder might improve kidney, liver and heart weight.

In the current study, the liver function markers were significantly increased in tramadol group compared with the normal control one. This increase could be attributed to increased lipid peroxidation in hepatic tissues, which affects the function and structure of cell membranes, leading to increased leakage of these enzymes from hepatocytes into the blood stream (Salahshoor *et al*., 2016). In this context, several researches reported that exposure to tramadol resulting in elevated liver enzyme activities (Barbosa *et al*., 2017). Atici *et al*. (2005) reported that Long-term tramadol use resulted in significant increases in serum LDH (lactate dehydrogenase), AST and ALT levels in rats. As the increased secretion of these liver enzymes is often accompanied with acute cell necrosis, the elevated plasma level of these enzymes in tramadol-treated rats could be attributable to necrosis or damage to the liver cell membrane, allowing the enzymes to escape into the blood stream (Loughrey *et al.*, 2003).

It was clear from the current investigation that administration of barley and wheat grasses improved liver parameters. Daily consumption of barley grass powder enhances liver function and immunity; has hypolipidemic and loses weight; anticancer and anti-inflammatory effects; prevents heart disease (Zuo *et al*., 2017).

Saponarin-rich barley sprouts protect the liver by reducing the inflammatory

response caused by alcohol consumption (Lee *et al*., 2016). Saponarin demonstrated antioxidation and hepatoprotection against CCl_4-induced liver injury in vitro and in vivo (Simeonova *et al*., 2014).

By activating nuclear factor erythroid 2-related factor 2 (Nrf2) and increasing glutathione synthesis, barley sprout extract protects liver cells from oxidative stress, inhibiting glutathione depletion and hepatic lipid build up, as well as reducing serum biochemical indicators of liver injury and inhibiting inflammatory responses (Lee *et al*., 2017).

Wheat grass juice has various enzymes that help to cleanse the body of toxins and pollutants, and amino acids help to detoxify the liver and eliminate toxic heavy metals from the blood stream, eliminate waste from the body, and slow down the ageing process (Sareen *et al*., 2014). It was documented that wheat sprouts produce some physiologically active phytochemicals during germination; wheat grass leaf extract impacts liver enzyme activity and lipid peroxidation (Calzuola *et al*., 2004). Fresh wheat grass juice had a hepatoprotective effect in CCl_4-treated rats. With a dose of 100mg/kg/day, it showed a strong hepatoprotective impact in terms of ALP, SGPT, SGOT and Bilirubin in serum (Jain *et al*., 2007). Kamboj *et al.* (2011a) reported that depending on the amount of wheat grass, it prevents a rise in liver enzymes.

Notably, the serum total protein, albumin and globulin (mg/dl) were markedly decreased in tramadol treated rats compared with the control group in the present study. In a tramadol-induced lethal overdose with liver failure, albumin levels were found to be lower (Loughrey *et al*., 2003). Also, serum albumin and total proteins were found to be lower in opium-addicted diabetic males (Asadikaram *et al*., 2004). Such results show that because these analytes are produced entirely or largely by the liver, the hepatic synthetic function is impaired (Yang *et al*., 2014). Khalaf (2017) reported that the due to oxidative stress and liver damage, tramadol treatment reduced total protein, albumin, and globulin levels**.**

In the present study, administration of barley grass and wheat grass increased the total protein, albumin and globulin in serum of rats. Increased protein may be due to phenols existing in the wheat grass might have successfully prohibited the cell membrane injury (Datta *et al*., 2012). Consumption wheat grass extract increased the total protein near normal (Lakshmi *et al*., 2015).

Tramadol's toxic action results in a high population of unquenched free radicals, resulting in oxidative stress. Inhibition of antioxidant enzymes catalase (CAT) and glutathione peroxidase (GPX) activities in serum of rats in this investigation supports this theory. The present study demonstrated that Tramadol induced hepatic oxidative damage by greatly increasing ($p<0.05$) lipid peroxidation (MDA), which was accompanied by a reduction in the activity of antioxidant enzymes GSH and CAT concentration. Tramadol or its metabolites may bind to transition metals, which act as cofactors for antioxidant enzymes, causing antioxidant enzymes to be inhibited (Abdel-Zaher *et al*., 2011). These findings were in agreement with the results of Barbosa *et al*. (2017). CAT, SOD and GSH are antioxidant enzymes that play a key role in the scavenging of oxidative free radicals (Kruidenier *et al*., 2003). The suppression of antioxidant enzymes identified in this study could be attributed to their exhaustion as a result of oxidative stress generated by tramadol administration. The current results agreed with those of Ahmed and Kurkar (2014), which indicated tramadol promoted lipid peroxidation and raised MDA levels. Awadalla and Salah-Eldin (2015)

documented that tramadol usage induced oxidative stress through increasing MDA level, decreasing the activities, of GSH, CAT and SOD enzymes in both liver and kidney tissues.

The present study found that administration of barley and wheat grasses (500 mg/kg) improved antioxidant enzymes in serum and liver tissues of male rats. Polyphenols, flavonoids, vitamins, and volatile compounds are all natural antioxidants found in plants (Moon and Shibamoto, 2009).

Barley is one of the most stress-tolerant crops, with the same genes encoding enzymes in the pathways that produce antioxidant metabolites in its flag leaf-tocopherol, glutathione, and succinate (Templer *et al*., 2017). Barley Superoxide dismutase, 2″-O-glucosyl isovitexin (2″-O-GIV), and protoheme are all antioxidant phytonutrients found in barley grass (Choe *et al*., 2010). Antioxidant flavonoids (saponarin and lutonarin) have been extracted from young barley grass, with saponarin and lutonarin levels increasing with UV exposure (Ferreres *et al*., 2008). Saponarin, found in barley grass, has potent antioxidant properties that can help prevent diseases induced by oxidative stress, such as cancer, inflammation, and liver disease (Kamiyama and Shibamoto, 2012). Barley grass has many health effects, such as hypoglycemic, anticancer and preventive constipation, antioxidant, and anti-inflammatory activities (Lahouar *et al*., 2015).

Wheat grass has many antioxidant compounds as selenium, provitamin A,C,E, Carotene, transhydrogenase and superoxide dismutase (SOD) cytochromeoxidase (Padalia *et al*., 2010). Wheat grass treatments have been shown to reduce oxidative stress and improve antioxidant levels (Kamboj *et al*., 2011b). Wheat grass has protective effect against the oxidative stress in diabetes ratseitherby preventing generation free radical or by stimulating endogenous antioxidant protection or both in body tissues (Shakya *et al.*, 2012). Wheat grass contains both of enzymatic and non-enzymatic antioxidants so; it reduced the oxidative stress (Sachin *et al*., 2013). Wheat grass contains great amount of antioxidants, thus it can be administered as an antioxidant phytomedicine to treat the oxidative stress caused by chemotherapy (Sachin *et al*., 2013). Durairaj *et al*. (2014) found that administration of wheat grass to male rats improved antioxidant levels such as catalase, superoxide dismutase, glutathione peroxidase, reduced vitamin C, vitamin E, and glutathione, which had been lowered due to oxidative stress caused by alcohol. Wheat grasses extract obviously normalized antioxidant enzymes in liver and kidney tissues by detoxification of body cells from free radical (Lakshmi *et al*., 2015).

Conclusions and recommendation

Tramadol has side effects that have caused oxidative stress and induced hepatotoxicity in the investigated male rats. Wheat and barley grasses can alleviate biochemical changes, oxidative stress, and hepatotoxicity induced by tramadol due to their content of polyphenols and other antioxidant compounds. However, these evidences have to be tested on human before giving any recommendation towards using barley and wheat grasses to protect human against the hepatotoxicity that can be produced due to long administration of tramadol.

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التأثيرات الوقائية لحشائش القمح والشعير على التسمم الكبدى المحدثبالترامادول في ذكور الجرذان

لمياء مصطفى عبد المولى
قسم التغذّية وعلوم الأطعمة ، كلّية الاقتصاد المنزلّى ، جامعة الأزهر،طنطا

المستخلص

حديثاً، أصبح استخدام الترامادول أكثر شيوعًا بين المراهقين في معظم البلدان في جميع أنحاء العالم،وخاصة بين الذكور. لذلك فأن الهدف من هذه الدراسة هوتقييم التأثيرات الوقائية لحشائش القمح و الشعير على السمية الكبدية التي يسببها الترامادول في ذكورالجرذان. تم تقسيم عدد ثلاثين من الجرذانالألبينو الذكور (150-200 جم) إلى مجموعتين رئيسيتين، المجموعة الرئيسية الأولى (5 جرذان) تم تغذيتها على النظام الغذائي الأساسى وتم الأحتفاظ بها كمجموعة ضابطة سالبة (G). بينما المجموعة الرئيسية الثانية (25 جرذ) تم تغذيتها على النظام الغذائي الأساسى واعطاؤها ترامادول (30 ملجم / كجم / يوم) عن طريق الفم لمدة 30يوم. بعد ذلك, تم تقسيم الجرذان إلى خمس مجموعات فرعية على النحو التالي: المجموعة الفرعية (1): تم الاحتفاظ بها على أنها مجموعة ضابطة موجبة (G +). المجموعات الفرعية (2 و 3) تم إعطائها ترامادول + حشيشة القمح (250 و 500 ملجم / كجم من وزن الجسم) والمجموعات الفرعية (4 و 5) تم إعطائها ترامادول + حشيشة الشعير (250 و 500 مجم / كجم من وزن الجسم) عن طريق الفم لمدة 30 يومًا، ومن ثم تم اجراء التقييم البيولوجي، و أخذ السيرم لاجراء التحاليل البيوكيميائية. أظهرت النتائج البيوكيميائية ارتفاع فى إنزيمات الكبد (الألانين أمينو ترانسفيراز ، الأسبارتات أمينو ترانسفيراز ، الألكالين فوسفاتيز)، البيليروبين الكلي، البيليروبين المباشر، البيليروبين غير المباشر وكذلك فى وزن الكبد في مجموعة الترامادول. كما لوحظ ايضا زيادة كبيرة في المالون داى الدهيد، أكسيد النيتريك. بينما كان هناك انخفاض كبير في مستويات الجلوتاثيون بيروكسيديز، الجلوتاثيون المختزل والكتاليز في مجموعة الترامادول (G +). وقد أثبتت الدراسة أن الاستخدام المتزامن لحشائش القمح والشعير مع الترامادول يؤدى الى حدوث تحسن فى التأثيرات السامة للكبد. تم تسجيل أفضل النتائج للمجموعات المعالجة بجرعة عالية من حشائش القمح و الشعير. نستنتج من نتائج هذه الدراسة أن الاستخدام المتزامن لحشائش القمخ والشعير مع الترامادول له القدرة على تخفيف التسمم الكبدى المحدث بالترامادول وربما يرجع ذلك الى ق درها المضادة للأكسدة.

الكلمات المفتاحية: التسمم الكبدى , الترامادول , انزيمات الكبد , انزيمات مضادات الأكسدة , حشيشة القمح , حشيشة الشعير.