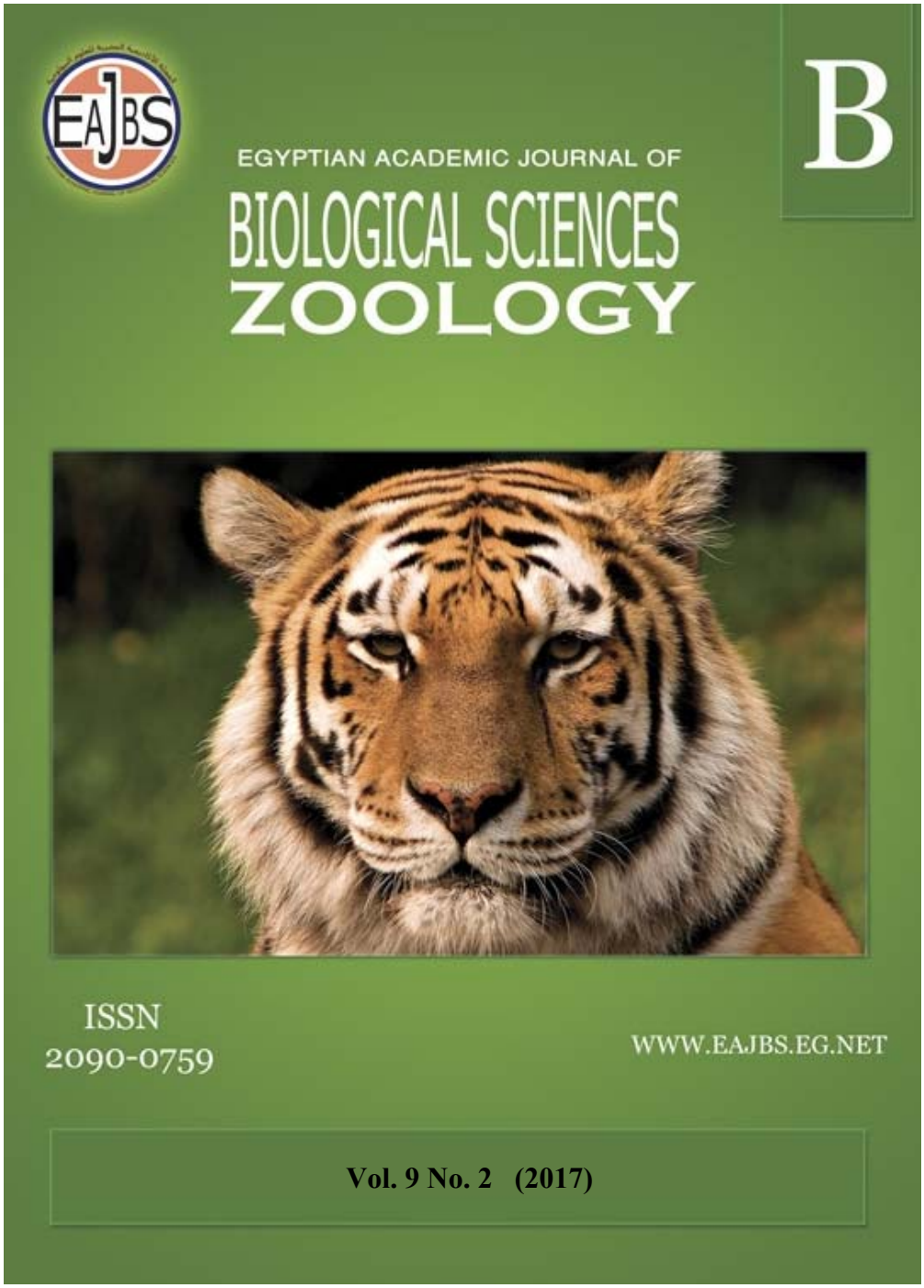

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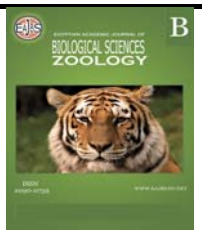

Efficacy of *Moringa oleifera* Aqueous Extract in Inhibiting Tamoxifen®-Induced Physiological Hepatic Deterioration in Male Albino Rats.

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ABSTRACT

Tamoxifen citrate (TAM) is a widely used drug in breast cancer treatment. It showed a degree of hepatic carcinogenesis. The purpose of this study was to elucidate the antioxidant capacity of *Moringa oleifera* aqueous extract (MAE) against TAM-induced liver injury. A model of liver injury in male rats was done by orally administration of TAM in a dose of 3mg/Kg/3days for consecutive six weeks to evaluate the drug-toxicity in combination with MAE in a dose of 300mg/Kg/day for similar period. The model of TAM-intoxication elicited significant elevation in serum alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) activities as well as hepatic levels of the oxidative stress markers (MDA and NO),lipid profiles and inflammatory marker(TNF-α) associated with a significant depletion of anti-oxidative marker (GSH).The oral administration of MAE in combination with TAM-intoxicated rats, resulted in significant improvements in ALAT,ASAT and anti-oxidative marker (GSH)with significant decrements in MDA, NO and lipid profiles. The data obtained from this study speculated that MAE has the capacity to scavenge free radical and can protect against oxidative stress induced by TAM intoxication. Supplementation of MAE could be useful in alleviating tamoxifen-induced liver injury in rats.

INTRODUCTION

Since ancient times, plants remained major natural resource in the world (Kalia, 2005); and these plants have a great demand in both developed and developing countries (Yirga *et al*., 2011). World Health Organization estimated that 80%world's population relies on traditional medicines to meet their primary health care needs, most types of which use remedies from plants. Even the modern pharmacopoeia still contains at least 25%of drugs derived from plants as it was suggest that over 9000 herbs have known medicinal applications among various cultures and countries (Kalia, 2005). Flavonoids have been found to play important roles in the non-enzymatic protection against oxidative stress (Okada *et al*., 2001; Babich *et al*., 2005), especially in case of cancer.

Moringa oleifera Lam is a well-known widely distributed species of Moringaceae family enriched with many bioactive compounds such as kaempferol, rhamnetin, quercitin, chlorogenic acid, rutin, apigenin that exhibit antimicrobial, anti-inflammatory, anti-cancer, anti-diabetic effects (Karthivashan *et al*., 2013; Ezuruike & Prieto, 2014, Anwar *et al*., 2007; Coppin *et al*., 2013) (Fig. 1). It has recently been evaluated for its hepatoprotective effects (Das *et al*., 2012; Sharifudin *et al*., 2012).

Tamoxifen citrate (TAM), 1-[4-(2-dimethyl-aminoethoxy) phenyl]-1,2-diphenyl-1-butene) (Fig.2) is a nonsteroidal antiestrogen drug that is used in the treatment and prevention of all stages of hormone-dependent breast cancer (Desai *et al*., 2002; Jordan, 2003). It is an orally available ER antagonist, which competitively blocks the binding of estrogen, such as 17b-estradiol (E2), to the receptor and is effective at treating breast cancer in pre- and post-menopausal women (Deroo *et al.*, 2006). Therapy using tamoxifen is often limited because Tamoxifen possesses agonistic effects in uterine cancer cells and increases the risk of endometrial and liver cancer. (Kedar*et al*., 1994;Shang &Brown., 2002).

It was revealed that, TAM in high dose is a known liver carcinogen in rats (Ahotupa *et al*., 1994; Calballero *et al*., 2001) which is due to oxygen radical overproduction which occurs during TAM metabolism. A high frequency of p53 mutations is detected in hepatocarcinomas induced by tamoxifen exposure (Vancutsem *et al*., 1994). TAM has been shown to potentiate lipid proxidation and nitrous oxide production in breast cancer patients through enhancement of nitric oxide synthase II expression (Simeone *et al*., 2002), therefore the aim of this work is to study antioxidant and improving potential of moringa oleifera aqueous extract against the Tamoxifen®-induced toxicities in male albino rats.

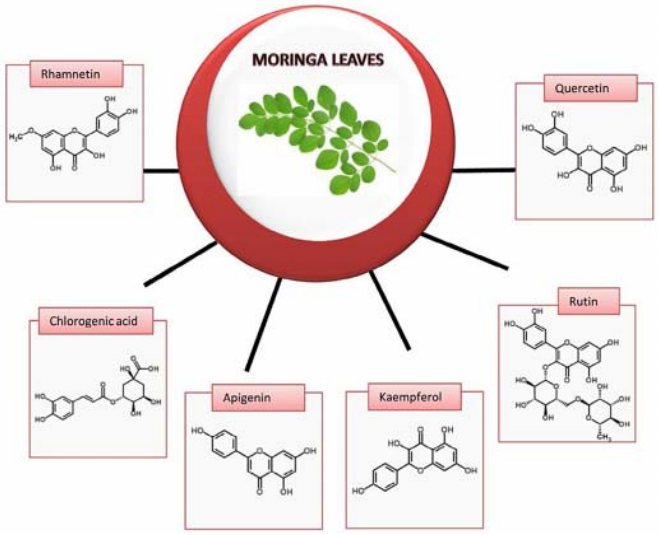

Fig.1- Major bioactive constituents of *Moringa oleifera* leaves, holding high therapeutic properties that supposedly act against Tamoxifen® induced hepatotoxicity.

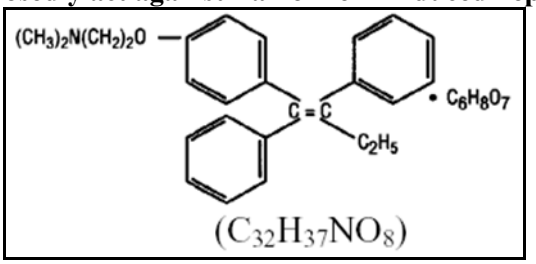

Fig.2- Chemical structure and empirical formula of Tamoxifen.

MATERIALS AND METHODS

Chemicals: Tamoxifen citrate (TAM), was a kind gift obtained from medical union pharmaceutical drug company (MUP), Egypt. All the other chemicals were of analytical grade and purchased from Sigma (St. Louis, USA) and Fluka (Buchs, Switzerlands).

Herb Extraction: Moringa (*Moringa oleifera*) herb was obtained from a local and clearly identified by a special botanist, faculty of pharmacy, Cairo University. The aqueous extract was carried out according to the method of Berkovich*et al.* (2013). 50 g of powdered dry herb leaves were soaked in 500 ml boiling distilled water for 15minutes; then filtered through sterile Whatman filter paper number 42 (Whatman International Ltd, Maidstone, England) and lyophilized (freeze drier, Snijders-Scientific-tilburg,Holland).

Extract yield :After lypholyzation, the aqueous extract yield was calculated according the equation :

[Extract yield percentage (g/g crude herb) = $(W_2-W_3)/W_1*100$; where, W_1 is the weight of clear and dry quick fit flask (grams), W_2 is the weight of the flask after lypholization (grams) and W_3: is the weight of the crude powdered herb in grams used in extraction process]

Determination of extract total phenolics contents:

The content of total phenolics compounds was evaluated spectrophotometrically by the modified method of Jayaprakasha *et al*. (2000). In brief, **5**mg of the extract was dissolved in a 10 ml mixture of acetone and water (6:4 v/v), then samples (0.2ml) were mixed with 1.0 ml of 10 folds diluted Ciocalteu reagent and 0.8 ml of sodium carbonate solution (7.5%). **A**fter 30minutes at room temperature, the absorbance was measured at 765 nm using spectrophotometer. The level of phenolic compounds as catechin equivalents (CE) was calculated from catechin standard curve.

Evaluation of extract radical scavenging activity (RAS):

The capacity of antioxidants in the extracts to quench DPPH radical was determined using the method of Nogala-Kalucka *et al.* (2005). Dissolve a certain weight of the extract in methanol (MeOH) to obtain a concentration of 200ppm; then 200µl from this solution was made up to 4ml by MeOH. Add 1 ml of DPPH solution ($6.09x10^5$mol/l, in MeOH), and after 10 minutes the absorbance of both tested and control samples [1ml of DPPH solution ($6.09x10^5$mol/l) mixed with 4 ml MeOH] was measured spectrophotometrically at 516nm; then RSA was calculated according to the following below.

$$RAS\% = \frac{\text{absorbance of control sample} - \text{absorbance of tested sample}}{\text{absorbance of control sample}} * 100$$

Animals:

Adult male Wistar albino rats weighting 120-150g were obtained from Animal House, National Research Centre, Giza, Egypt and housed in suitable plastic cages for one week for acclimation. Excess tap water and standard rodent food were always available. All animals were received human care in compliance with the standard institutionals' criteria for the care and use of experimental animals as cited by animal ethical committee number FWA00014747

Experimental design:

After acclimatization, animals were arranged randomly into 4 groups (10 animals each) as 1) normal animals fed normal diet and acting as control, 2) normal animals administrated orally with 3mg/kg/3days of Moringa aqueous extract (MAE)

for 45 days (Jaiswl *et al.,* 2009), 3) animals administrated orally with 3mg/kg/day anticancer drug (Tamoxifen®-20mg; AMRIYA Pharmaceutical Industries, Amriya, Alexandria City, Egypt) for 45 days *(pala et al., 2015)*, and finally group 4) animals subjected to daily oral administration of MAE for 45 consecutive days before oral ingestion with Tamoxifen® for the same duration.

Body weight gain:

Body weights were recorded at the begin and end of the experiment; consequently the percentage of weight gain was calculated according to the formula:

[body wight gain (%) = $\frac{W2-W1}{W1} * 100$; where W1 is the animals' weight at start, W2 is the animals' weight at the end of the experiment].

Blood sampling:

At the end of the study period, animals were fasted overnight, and following diether anesthesia, blood specimens were drawn, left to clot and centrifuged; the sera were separated, divided into aliquots and stored at -70°C.

Tissue sampling:

After blood collection, all animals were rapidly sacrificed and the liver left lobe of each animal was dissected, washed with saline, dried, rolled in a piece of aluminum foil and stored at –70 °C until homogenization and biochemical determinations.

Tissue homogenate:

A specific weight of each liver subjected to homogenization in ice-cold phosphate buffer (50 mM, pH 7.4) to give 10% homogenate (w/v); the homogenates were centrifuged at 9000rpm for 20min and each supernatant was divided into aliquots and stored at -70°C for biochemical measurements.

Biochemical analyses:

All the biochemical measurements were carried out using UV-Visible spectrophotometer (Schimadzu spectrophotometer 1201, Japan). Activity of serum aminotransferases (ALAT & ASAT) was determined according to the colorimetric method described by Dufor *et al.* (2010) and Berth & Delanghe (2004) respectively using reagent kits obtained from Biodiagnostic, Egypt. Serum levels of lipid profile was determined colorimetrically using kits purchased from ELITech Clinical Systems SAS–Zone Industrielle – 61500 SEES France. Blood glucose level was estimated colorimetriclly using reagent kits obtained from Biodiagnostic Co., Dokki, Giza, Egypt**.** Serum TNF-α was estimated according to the manual instruction of ELISA kit purchased from Gloury, while USA, Total antioxidant capacity (TAC), nitric oxide (NO), reduced glutathione (GSH) of liver homogenate was estimated spectrophotometrically using reagent kits obtained from Bio-diagnostic Co., Dokki, Giza, Egypt.

Histopathological analysis:

Another portion of each liver was preserved in formalin-saline buffer (10%) for 24 hours; then washed in tap water overnight followed by dehydration in graded alcohol, clearing in xylene for 20 minutes and embedded in paraffin wax. Transverse serial sections were then cut at 5 micrometers thickness and mounted on albumenized slide. Sections were stained with hematoxylin and eosin (Drury & Wallington, 1980) and investigated by light microscope.

Statistical analysis

The obtained data were subjected to one way ANOVA followed by post hoc test (Duncan) at a probability level $p \leq 0.05$ (Steel & Torrie, 1960). ANOVA was carried out using statistical analysis system (SAS) program software; copyright (c) 1998 by SAS Institute Inc., Cary, NC, USA.

RESULTS

Our study was carried out to evaluate the Efficacy as well as its antioxidant and ameliorative potential. In this study, the *in vitro* measurements (yield, total phenolic compounds (TPC) and radical scavenging activity (RSA) recorded that MAE possesses a high yield, RSA and TPC higher values (Table 1). This finding confirmed a previous study of Santos *et al*. (2012). Also, the results declared that body gain (Table 2) in rats treated with MAE alone did not disturbed from normal animals, evidencing its safe effect on the body weight, while animals those were intoxicated with the anti-cancer drug (Tamoxifen®) showed a significant reduction in body weight gain. Fortunately, the body weight gain of animals those were administrated with TMX and MAE either in combination, one before the other significantly increased in compare to those administrated with TMX alone. TMX then MAE together recorded the highest degree of improvement in body weight gain, proving that MAE possesses a preventive potential against weight loss.

Table1. Mean values of yield, total phenolic content (TPC) and radical scavenging activity (RSA) of aqueous extract of *Moringa olifera* leaves.

	Moringa aqueous extract
Yield (g %)	12.13 ± 0.27
TPC (mg/g)	1.38 ± 0.38
RSA (%)	68.70 ± 2.41

All values are represented as means ± standard error for 3 replicates measurements.

Table2. Effect of oral administration of aqueous extract of *Moringa olifera* on body weight gain of treated and control rats (*Rattus norvigicus*).

	Body Weight Gain (g/100g b.w)
Control	57±2.13
MAE	61±3.05
TMX	32±2.85 ^{A}
TMX then MAE	48±1.21 $^{\#}$

Data are expressed as mean ± standard error.
Data were subjected to student t-test statistical analysis.
MAE (Moringa aqueous extract), TX (Tamoxifen®), ^{A}(significant from control), ^{B} (significant from TX).

With regard to Tables (3), the data revealed that administration of rats with MAE didn't disturb the level of hepatic function (ALAT and ASAT),inflammatory marker (TNFα) and glucose level evidencing its safety; while ingestion of Tamoxifen led to a significant deterioration in this parameters when both groups were compared to normal one.

In comparison with Tamoxifen®-treated group, administration of Tamoxifen® then MAE (therapeutic group) resulted in a significant improvement in hepatic functions as well as inflammatory marker (TNFα) and glucose levels.

Table 3. Effect of oral administration of aqueous extract of *Moringa olifera* on the levels of serum ALAT, ASAT, TNF-α of control, intoxicated and treated male albino rats.

	ALAT IU/L	ASAT IU/L	TNFα ng/L	Glucose
Control	72 ±2.9^{B}	125 ± 4^{C}	53±3.9^{C}	91±6.2^{A}
MAE	71±2.8^{B}	120 ± 4 ^{C}	52±3.9^{C}	94±4.9^{A}
TMX	106±7.^{A}	222 ±11^{A}	93±6.9^{A}	84±5.7^{A}
TMX then MAE	82.3±14.5^{B}	163±33.4^{BC}	82±6.1^{B}	87±5.9^{A}

All data are expressed as mean ± slandered error (M±SE).
Data were subjected to analysis of variance (ANOVA) post hoc (Duncan) statistical analysis at $p \leq 0.05$ level.
Means with different superscript letters are significantly different at $p \leq 0.05$.
MAE (Morenga aqueous extract) and TX (Tamoxifin® drug).

The results of lipid profile in Table (4) illustrated that administration of rats with MAE similarly didn't unfavorably serum total cholesterol, triglycerides, LDL or HDL; in contrast, Tamoxifen®-intoxication led to a significant increase in the total cholesterol, triglycerides and LDL matched with a marked disturbance in HDL level when both groups were compared with normal control. Moreover and compare to Tamoxifen®-treated group, animals treated with MAE after Tamoxifen® showed a significant reduction in cholesterol, triglycerides and LDL coupled with a slight elevation in HDL.

Table 4. Effect of oral administration of aqueous extract of *Moringa olifera* on the levels of serum lipid profile of control, intoxicated and treated male albino rats.

	Cholesterol mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl
Control	85±3.9^{D}	78±2.9^{C}	39±2.7^{C}	30±3.9^{AB}
MAE	86±3.9^{D}	73±2.5^{C}	38±2.6^{C}	32±4.0^{A}
TMX	123±5.6^{A}	121±4.2^{A}	67±4.5^{A}	20±1.4^{C}
TMX then MAE	108±4.9^{BC}	106±3.7^{B}	59±3.9^{B}	23±1.7^{BC}

The obtained results in Table (5) showed no unfavorable changes in the hepatic oxidative status; however the intoxication with Tamoxifen® drug resulted in high marked elevation in hepatic levels of MDA and NO associated with a significant depletion of GSH. On the other side and in compare to Tamoxifen® group, treatment of animals with Tamoxifen® followed by MAE induced a marked decrement in the oxidative stress markers (MDA and NO) and concomitant with obvious improvement in the anti-oxidative marker (GSH).

Table 5. Effect of oral administration of aqueous extract of *Moringa olifera* on the levels of hepatic MDA, NO and GSH of control, intoxicated and treated male albino rats

	MDA mmol/g	NO mmol/g	GSH mg/g
Control	107±4.1^{C}	54±3.7^{C}	63±2.3^{B}
MAE	105±4.1^{C}	52±3.5^{C}	65±2.5^{B}
TMX	153±5.9^{A}	73±5.0^{A}	48±1.7^{C}
TMX then MAE	133±5.1^{B}	64±4.4^{BC}	55±2.0^{C}

DISCUSSION AND CONCLUSION

Cancer is considered a public health problem in developed and developing countries (Guerra *et al*., 2005; Pedroso *et al*., 2013). Tamoxifen (TMX), a selective estrogen receptor modulator and non-steroidal antiestrogenic drug, is used in the chemotherapy of breast cancer (Kuo *et al*., 2012; Tsai *et al*., 2014; Pandey *et al*., 2016) but many studies reported that tamoxifen in toxic doses lead to oxidative liver damage (Hard *et al*., 1993) and its adverse effects, such as hot flashes, fatty liver, hepatotoxicity and hepatocarcinomas (Ribeiro*et al*., 2014; Wickramage *et al*., 2017).It may be more toxic to liver because it has higher affinity for hepatic tissue than for any other tissues (Desai *et al*., 2002), therefore this study was conducted in order to investigate the role of MAE, as food supplement or pro-drug, in reducing Tamoxifen® side effects through studying of its antioxidant and protective potential against the Tamoxifen-induced toxicities in male albino rats.

In accordance with the data obtained from this study, TMX administration resulted in decrease in the body weight gain. The loss in the body weight gain, from our point of view, may be due to the disturbance in the animals' appetite, digestive system physiology, food absorption and food assimilation as a consequence to Tamoxifen®, but animals' those were treated with MAE after TMX recorded a significant improvement in the body weight gain in compare to the Tamoxifen®-intoxicated group.

Our results showed that intoxication with Tamoxifen® only showed a significant elevation in ALAT and ASAT activities .One or more mechanism could explain the Tamoxifen®-induced hepatic disorder where Tamoxifen® causes mitochondrial dysfunction (Farrell, 2002; Larosche *et al*., 2007; Patel &Sanyal, 2013). Mitochondrial damage and the resultant inhibition of the electron transport chain result in the formation of ROS, which react with poly unsaturated fatty acid(PUFA) to produce lipid peroxidation products, which damage the liver (Patel & Sanyal, 2013). These ROS can react with the lipid bilayer of the hepatocyte resulted in disturbance in the cellular integrity as well as permeability; therefore, elevated serum levels of ALAT and ASAT herein may be due to increase in the permeability of the cell membrane resulting in leakage of transaminases into the blood stream (Naik, 2010; Wickramage *et al*., 2017).The oxidation process that occurs as a result of TMX intoxication leads to release of iron ions. These ions become more reactive in liver; free iron ions participate in generation of hydroxyl radicals which are the most active reactive oxygen species (ROS) and they react readily with most cellular components (Ostrowska *et al*., 2004).

The serum levels of ALAT and ASAT were significantly decreased in therapeutic comparable to TMX-intoxicated group. Co-administration of Moringa extract as a food supplementation significantly reduced Tamoxifen-induced elevation of ASAT and ALAT activities that may be attributed to the stabilizing ability of the cell membrane preventing enzymes leakages as earlier, reflecting the protective effect on TMX-induced liver injury postulated by Pari and Karthikesan (2007). Also, the intoxication with Tamoxifen® drug led to the levels of oxidative stress markers (MDA and NO) in liver homogenates were significantly increase matched with a significant reduction in the anti-oxidative marker (GSH), whereas their levels were significantly improved upon treatment of MAE after Tamoxifen® administration. The detoxification of different drugs and xenobiotics in the liver involves reduced glutathione (GSH) in its detoxifying pathway (Seven *et al*., 2004).

Tamoxifen is hydrophobic and it accumulates rapidly in phospholipid bilayers of membranes where it is postulated to induce oxidative stress (Gundimeda *et al.*, 1996). Reduced glutathione (GSH), a universal antioxidant, is synthesized in the cytoplasm and then transported into mitochondria; the mitochondrial pool of glutathione is critical in maintaining the functional competency of the organelle and for cell survival (O'Donovan *et al*., 2011). The thiol group of GSH is a favored target during oxidative stress (Zaman *et al*., 1999). Moreover and accordance with the data obtained from this study, Stanley *et al*. (2001) and El Beshbishy (2005) reported that TMX administration resulted in significant increase in thiobarbituric acid reactive substances (TBARS) production; lipid peroxidation may be attributed to the fact that hexose monophosphate shunt (HMP) in rat liver is strongly inhibited by high dose of TMX, so that the NADPH levels inside cells is decreased. The state of oxidative stress observed during TMX administration in high dose was accompanied by decreased hepatic glutathione content and increased peroxidation (Ahotupa *et al*., 1994).

Also, it was reported that, due to liver damage, there was an observed decrease in antioxidant defenses in the liver (Seven *et al*., 2004). The impaired regeneration of protective and antioxidants such as reduced glutathione also contribute to oxidative stress (Sun *et al*., 1999). The decrease in antioxidant defense systems of TMX-intoxicated rats render them more susceptible to hepatotoxicity (Palomero *et al*., 2001). GSH plays a common role in cellular resistance to oxidative damage as a free radical scavenger as protein-bound glutathione and by generation of ascorbate or tocopherol in liver (Mark *et al*., 1996). The decreased hepatic GSH in TMX-intoxicated rats could be a result of hexose monophosphate (HMP) shunt impairment and thereby NADPH availability is reduced and the ability to recycle the oxidized glutathione disulfide (GSSG) to the reduced glutathione (GSH) is decreased (Lu, 1999). However, *M. oleifera* -treated rats was evoked to increase reduced glutathione level. It was suggested that aqueous extract of dried *M. oleifera* leaves containing 2,2-diphenyl-1-picrylhydrazyl with superoxide, hydroxyl radical scavenging activity favoring inhibition of lipid peroxidation. As well as, phenol and flavonoids content (Dasgupta & De, 2007). Also, it was illustrated that *M oleifera* is beneficial to protect liver from necrotic injury and fibrosis in rat model (Ndiaye *et al*., 2002).

The present investigation shown that rats treated with Tamoxifen® alone showed a disturbance in lipid profile pointed with a significant elevation in the serum level of total cholesterol, triglycerides and LDL-c associated with a duration-dependant decrease in the serum level of HDL-c but administration of Tamoxifen® followed by MAE showed a marked improvement in serum lipograme .The elevated total cholesterol level herein may be attributed to one or more, of the following explanations. Intoxication with Tamoxifen® may cause centrilobular necrosis, which results in translocation and accumulation of fats from peripheral adipose tissue into the liver, increases hepatic synthesis of fatty acids, impaired the function of smooth endoplasmic reticulum and induce peroxisomes to catalyze β-oxidation of fatty acids converting them into Acetyl-CoA, the precursor of cholesterol biosynthesis, and decreases the release of lipoproteins. Also, Tamoxifen® may activate the rate limiting enzyme, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which converts HMG-CoA into mevalonate which is the precursor of cholesterol biosynthesis (ref).

The elevation of triglycerides level may be due to impaired removal and destruction of TG rich in lipoproteins such as VLDL, LDL, IDL and remnants (Recknagel& Lombardi, 1961), this could be confirmed by the elevated level of LDL-c, or may be to the increased hepatic synthesis of fatty acids (precursors of TG formability).It was reported that apoprotein-B 100 (Apo-B 100; the essential structural

component of very low density lipoproteins, intermediate density lipoprotein and low density lipoproteins) is required for the intracellular assembly and secretion of these lipoproteins (Romero *et al.,* 2012); therefore, the elevation in LDL level herein could be attributed to the increased hepatic secretion of apoprotein B-100 which induced by Tamoxifen®. Also, the observed reduction in HDL after ingestion of Tamoxifen® in this study may be related to 1) the reduction in Apo-A1 (principle protein of HDL-c) or impaired synthesis of HDL; 2) its conformational changes or 3) the elevated level of hepatic lipase (HL) which has an inverse correlation with HDL-c that arises from the involvement of HL in the uptake of HDL by the liver and steroid secreting tissues (Colvin *et al.,* 1990). However, improvement in serum lipograme due to the inhibitory and modulatory effects of MAE against the changes induced by Tamoxifen® could be returned back to the antioxidative and radical scavenging properties of *Moringa oleifera* constituents that able to reduce the centrilobular necrosis and prevent translocation and accumulation of fats in the liver. Increased TG could cause the liver to form other types of lipids particularly the phospholipids (Guyton *et al.,* 2004).The obvious significant decrease in the HDL-C with a concomitant significant increase in the LDL-C level in tamoxifen- intoxicated group indicates a significant shift towards formation of bad cholesterol (LDL-C) but the addition of *Moringa oleifera* extract was seen to reverse this shift in therapeutic group thereby stabilizing the production of good cholesterol (HDL-C). Clinically, increased HDL is beneficial to health since it reduces the risk of coronary heart disease (Mayes, 1996). LDL-C is known to be the primary marker for a number of degenerative diseases, particularly arteriosclerosis (Mukherjee & Mitra, 2009).

The presence of phytochemicals in the *Moringa oleifera* such as glucosinolates, flavonoids and phenolic acids may have mopped up the free radicals produced by tamoxifen (Bennett *et al*., 2003; Kasolo *et al*., 2010; Amaglo *et al*., 2010) restoring an improved HDL-C level as seen in treated group where HDL-C removes deposition of cholesterol from the artery walls and returns them to the liver where they are broken down and eliminated from the body (Zhang *et al*., 2003).In addition, Ghasi *et al*. (2000) has reported that Moringa contains beta-sitosterol which lowers blood cholesterol in rat.

Our results declared that an inflammatory marker (TNF-α) showed a significant increase animals intoxicated with Tamoxifen® only but upon treated group with MAE showed a significant improvement in serum TNF-α Tamoxifen® was shown to induce reactive oxygen species (ROS) and oxidative stress in breast cancer cells, hepatoblastoma cells, retinal cells and platelets through activation of NAD(P)H oxidase, the enzyme that also promotes ROS production in macrophages (Forman & Torres, 2002; Cho *et al.,* 2012; Shah *et al*., 2012). ROS elevation or oxidative stress increases TNF-α production (Esposito *et al*., 2002). The increase in TNF-α has been reported to be mediated by reactive oxygen species via activation of transcription factors nuclear factor-κB (NF-κB) and activating protein-1(Guha *et al*., 2000).

The results achieved from this study declared that, the oral administration of MAE combined with TMX-intoxicated rats, exerted an improvement against Tamoxifen® hepatotoxicity as it have beneficial effects on damaged liver cells to prevent lipid peroxidation and improve anti-oxidative and an inflammatory markers. Also, the results further validate the notion that *usage of Moringa oleifera* after Tamoxifen® chemotherapy is advantageous, at least for reducing drug toxicity.

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ARABIC SUMMERY

فعالية المستخلص المائي للمورينغا أوليفيرا في تثبيط التاموكسيفين التي يسبب تدهورفي وظائف الكبد الفسيولوجية في الفئران البيضاء.

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يستخدم التاموكسيفين على نطاق واسع لعلاج سرطان الثدي وأظهرت درجة من التسرطن الكبدي لذلك الغرض من هذه الدراسة توضيح قدرة مضادات الأكسدة للمستخلص المائي لللمورينغا ضدسميه الكبد الناتجه عن التاموكسيفين.قد تم إجراء نموذج لإصابة الكبد في ذكور الفئران بتجريع التاموكسيفين بجرعة ٣مللي جم / كغ / ٣ أيام لمدة ستة أسابيع متتاليةعن طريق الفم لتقييم المخدرات السامة في تركيبة مع مستخلص المورينجا بجرعة ٣٠٠مللي جم / كغ / يوم لفترة مماثلة . وقد أدى نموذج التسمم بالتاموكسيفين إلى ارتفاع معنوي في الانزيمات الناقله لمجموعه الامين (الالانين والاسبارتيك)والدهون،بالاضافه الي مستوي اكسيد النيتريك ،مستوي الاكسده الفوقيه للدهون (المالوندايالدهيد)،الجلوتاثيون المختزل. قد أدى العلاج بمستخلص المرينجاإلى تحسينات كبيرة في الالانين والاسبارتيك و الجلوتاثيون المختزل مع انخفاض كبير مستوي اكسيد النيتريك ،مستوي الاكسده الفوقيه للدهون (المالوندايالدهيد).النتائج التي تم الحصول عليها من هذه الدراسة أثبتت ان المورينجا لديها القدرة على امساك الشوارد الحرة ويمكن أن تحمي من الإجهاد التأكسدي الناجم عن التسمم بالتاموكسفيين .