International Journal of Research in Medical Sciences
Ali FT et al. Int J Res Med Sci. 2016 Apr;4(4):1147-1153
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20160799

Research Article

Hepatoprotective and antiproliferative activity of moringinine, chlorogenic acid and quercetin

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Received: 04 February 2016
Revised: 03 March 2016
Accepted: 07 March 2016

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ABSTRACT

Background: The three well-characterized phytochemicals in *Moringa oleifera* leaves are moringinine, quercetin, and chlorogenic acid. *Moringa oleifera* is postulated to have the highest antioxidant content in food and also has a remarkable range of medicinal uses and high nutritional value.
Methods: Evaluation of the antiproliferative effect of moringinine, quercetin and chlorogenic acid as well *Moringa oleifera* leaves extract on two human cell lines, breast cancer cell line (MCF7) and liver carcinoma cell line (HepG2) using the sulforhodamine B (SRB) assay. The efficacy on liver toxicity induced in rat by alloxan was carried out.
Results: Our results indicated that both quercetin and moringinine are strong antitumor agents against the two human cell lines, the extract and its three active ingredients improved the induced liver toxicity.
Conclusions: Quercetin and moringinine are responsible to a great extent for the antitumor activity of the whole extract. Chlorogenic acid is a potent hepatoprotective in alloxan induced liver toxicity.

Keywords: *Moringa oleifera*, Quercetin, Moringinine, Chlorogenic acid, Antitumor effect

INTRODUCTION

Moringa oleifera (*M. oleifera*) Lam. (local name Sajna) belongs to the *Moringaceae* family. It is a multipurpose tree widely distributed around the world.[1]

Moringa oleifera, native of the western and sub-Himalayan tracts, India, Pakistan, Asia, Africa and Arabia, is now distributed in the Philippines, Cambodia, Central America, North and South America and the Caribbean Islands. Cultivation in Hawaii, for commercial distribution in the United States, is in its early stages. India is the largest producer of *Moringa*, with an annual production of 1.1 to 1.3 million tons of tender fruits from an area of 380 km² in some parts of the world.[2]

Moringa oleifera is valued mainly for the young leaves and tender pods which are esteemed as very common vegetable in Bangladesh and India. It is reported that *Moringa* leaf is a potential source of natural antioxidants such as total phenolics and vitamin A, C and E, ascorbic acid oxidase, polyphenol oxidase and catalase. The leaves are a rich source of essential amino acids such as methionine, cysteine, tryptophan, lysine, vitamins and minerals.[3] In the Philippines, it is known as 'mother's best friend' because of its utilization to increase woman's milk production and is sometimes prescribed for anemia.[4]

Moringa leaves have been reported to act as a hypocholesterolemic agent, thyroid hormone regulator, antidiabetic agent, antitumor agent and hypotensive agent.[5]

Of major medicinal interest are three structural classes of phytochemicals: glucosinolates, flavonoids, and phenolic acids.[6] Quercetin (flavonol) is a potent antioxidant with multiple therapeutic properties.[7,8] It has shown

antidyslipidemic, hypotensive, and anti-diabetic effects in the obese Zucker rat model of metabolic syndrome.[9]

Chlorogenic acid, which is an ester of dihydrocinnamic acid (caf-feic acid) and quinic acid, is a major phenolic acid in *M. oleifera* leaves.[10] The alkaloid moringinine is also present in leaves. This substance was suspected to mediate the hypoglycemic effect of the plant.[11]

There is increasing attention on natural products and the advantages of oral administration of anticancer drugs. Sreelatha et al reported that *M. oleifera* leaf extracts has potential for cancer chemo-prevention and can be claimed as a therapeutic target for cancer.[12]

Soluble extracts from *M. oleifera* leaves have been prepared and their potential, and three of its active ingredients, as new anticancer drug candidates has been assessed in this study. This study also aimed to investigate the efficacy of *M. oleifera* on liver toxicity induced by alloxan in rat model.

METHODS

All tested compounds were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other basic reagents were of analytical grade.

Preparation of *Moringa oleifera* leaf extract was prepared as described by Fahmy et al.[13]

Cytotoxicity determination

Human tumor cell lines (HepG2 and MCF7) were obtained frozen in liquid nitrogen (-180°C) from the American type culture collection. The tumor cell lines were maintained in the National cancer institute, Cairo, Egypt, by serial sub-culturing.

Human hepatoma cells (HepG2) and human breast cancer cells (MCF7) maintained in Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 unit/ml of penicillin G and 100 mg/ml of streptomycin sulfate) and cultured at 37 °C in 5% CO_2. Confluent grown cells will be harvested by trypsinization, collected into DMEM containing 10% FBS.

Cell proliferation assay

Cell culture cytotoxicity assays were carried out using the sulforhodamine B (SRB) assay. Cells were seeded in 96-well microliter plates at a concentration of 5x 104–105 cell/well in a fresh medium and left to attach to the plates for 24 h. Growth inhibition of cells was calculated spectrophotometrically using a standard method with the protein-binding dye sulforhodamine B [14]. The optical density (OD) of each well was measured at 564 nm with an ELIZA microplate reader (Meter Tech. Σ 960, USA). The percentage of cell survival was calculated as follows:

$$\text{Survival fraction} = \frac{OD\ of\ treatment\ cells}{OD\ of\ control\ cells}$$

The IC50 values were calculated using sigmoidal concentration– response curve fitting models (sigma plot software). The IC50 value is the concentration of tested compound, required to produce 50% inhibition of cell growth.

Experimental animals

Eighty five Wistar male rats weighed (185-200 g) were purchased from Egyptian rrganization for biological products and vaccines (Helwaan Farm). Rats had free access to commercial pelleted diet and tap water before the start of the experiment (five per cage) and were provided a 1-week acclimatization period.

After 12h fasting, rats intra-peritoneally injected with freshly prepared alloxan (120 mg/kg body weight, dissolved in 0.9% saline).[15] After 48h of alloxan treatment, rats with marked hyperglycemic (fasting blood glucose >200 mg/ dl) were selected, then divided into five groups (15 rats) and 10 rats were run along experiment as control.

Group (1): normal control rats, group (2): Rats supplied with alloxan only (120 mg/kg), group (3): Rats treated with alloxan, then treated with leaf extract at dose of (150 mg/Kg/day) for 21 days, group (4): Rats treated with alloxan, then orally administered with moringinine at dose of (3600 µmole/Kg/day) for 21 days, group (5): Rats treated with alloxan, then orally administered with quercetin at dose of (30 mg/Kg/day) for 21 days and group (6): Rats treated with alloxan, then orally administered with chlorogenic acid at dose of (10 mg/Kg/day) for 21 days.[16-19] At the end of the experiment animals, which survived (seventy four), were sacrificed by decapitation after overnight fasting and blood samples were collected in dry clean glass tube without additives to clot at 37ºC for 20 minutes, and then centrifuged at 3000 rpm for 10 minutes.

Colorimetric determination of ALP was carried out according to the method of King& Armstrong, using kit from spectrum diagnostics, Egypt.[20]

Protein determination was carried out by the method of Bradford, using Kit (spectrum diagnostics, Egypt).[21]

Autopsy samples were taken from liver of different groups; fixed, washed and stained by hematoxylin and eosin stains for histopathological examination by the electric light microscope. [22]

RESULTS

Figure 1 shows the *in vitro* cytotoxicity of the extract and its active ingredients (moringinine, quercetin and chlorogenic acid) using HepG2 cell line. The IC50 values, the concentration that inhibited 50% of the cellular proliferation, of the compounds are also shown in the same figure.

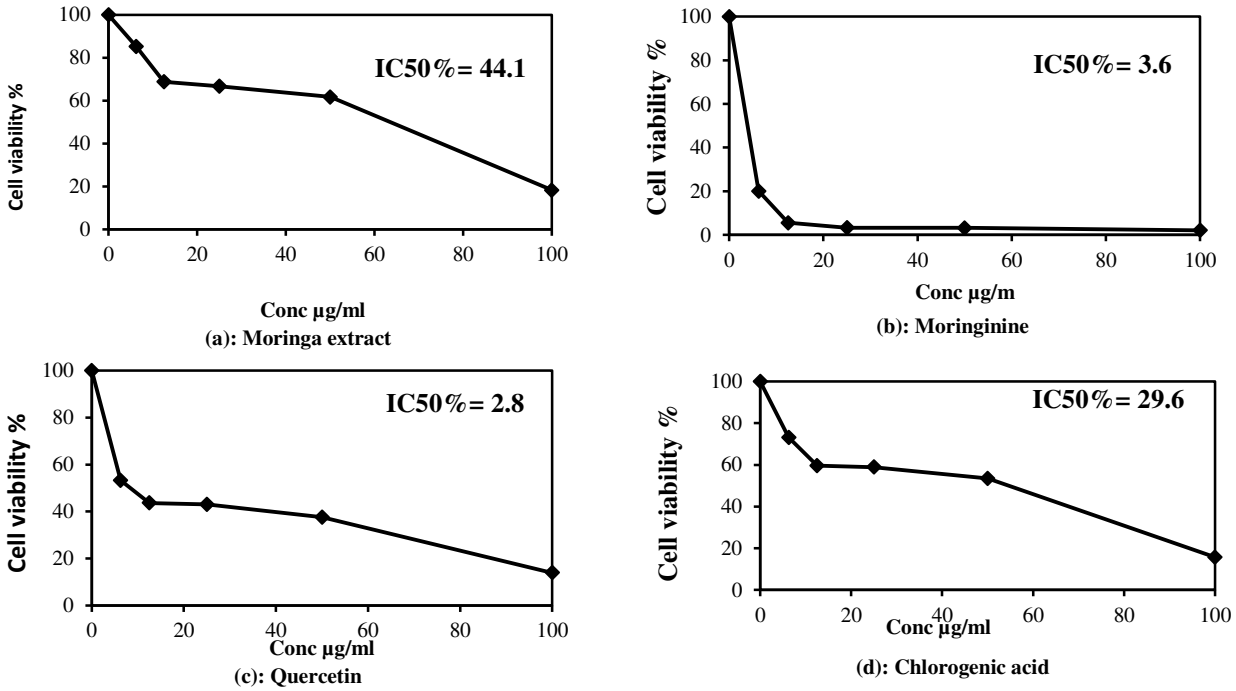


Figure 1: The in vitro cytotoxicity results of mol extract and its active ingredients using human liver carcinoma cell line ($HepG_2$).

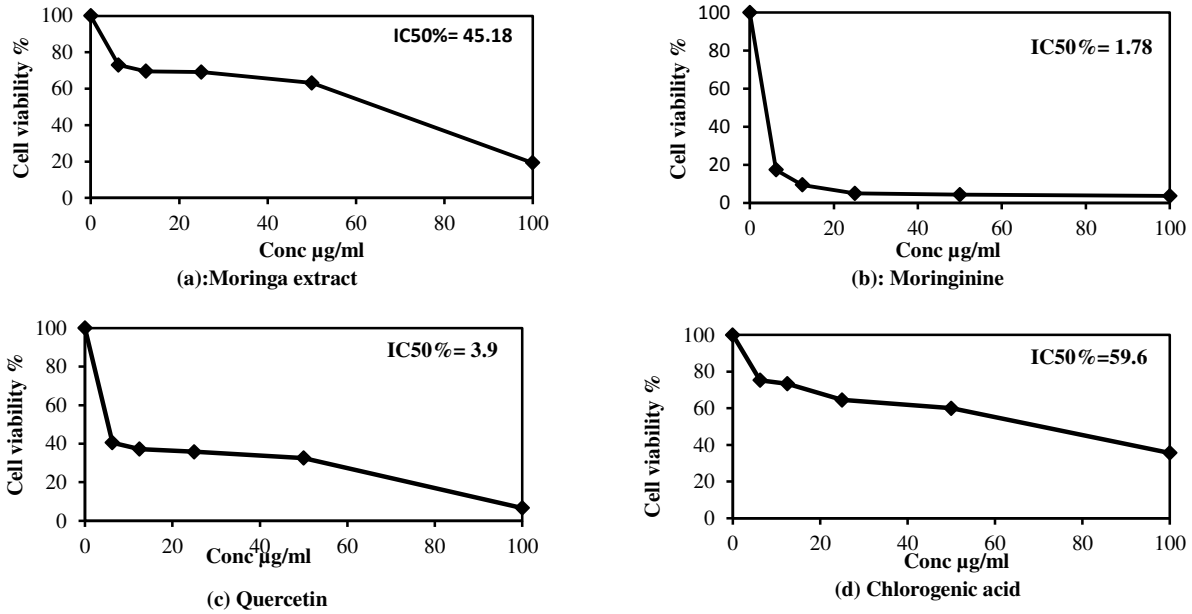
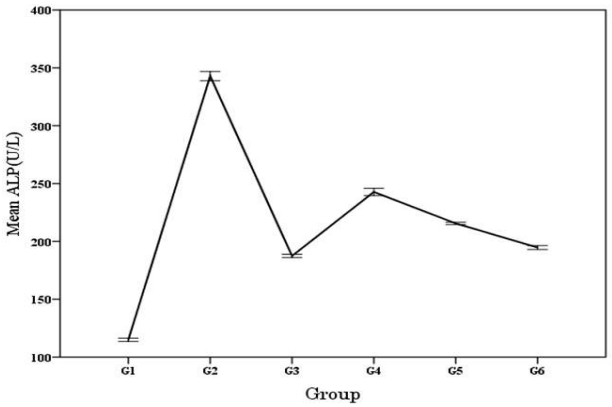


Figure 2: The in vitro cytotoxicity results of MOL extract and its active ingredients using human breast carcinoma cell line (MCF-7).

Results in Figure 2 shows the cytotoxic effect of *M. oleifera* extract and the other three ingredients on the breast human carcinoma cell line (MCF-7) and also the IC50 values for all the tested compounds.

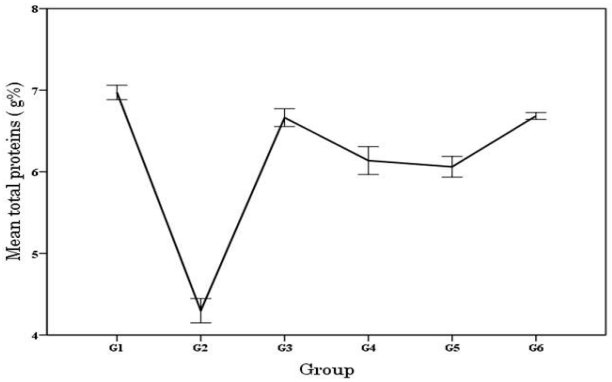
The activity of alkaline phosphatase (ALP) was highly significant increase in group 2 compared to control group, while the level of total protein decreased significantly. Meanwhile in all other treated groups, the administration

of the *M. oleifera* extract and the other bioactive compounds significantly normalize the ALP activity by (62.9%) in group 3, (111%) in group 4, (87.4%) in group 5 and (69.3%) in group 6. While total protein shows non-significant change in groups 3 and 6 and improved in groups 4 and 5 by (-11.9%) and (-13.9%) respectively. Data of Figures 3 and 4 revealed that, *M. oleifera* leaf extract has greater efficacy to normalize the liver function tests than each individual compound.



G1: Normal control; G2: alloxan group; G3: treated with extract; G4: treated with moringinine; G5: treated with quercetin; G6: treated with chlorogenic Acid.

Figure 3: Mean±SE of ALP in all groups.



G1: Normal control; G2: alloxan group; G3: treated with extract; G4: treated with moringinine; G5: treated with quercetin; G6: treated with chlorogenic acid.

Figure 4: Mean ±SE of total protein in all groups.

The anti-diabetic and the antioxidant effect of all the tested compounds were reported in our early study (Fahmy et al).[13]

Liver of rats in group (1) showed normal histological structure of the central vein and surrounding hepatocytes in hepatic parenchyma (Figure 5a). Figure 5b for liver of rats in group (2) showed dilatation in central vein and massive number of inflammatory cells infiltration in portal area. Fibrosis in portal area in the same group was shown in (Figure 5c), Figure 5d showed thickening in hepatic capsule by fibrosis and inflammatory cells infiltration in group (2).

Liver of rat in group (3) showed dilation and congestion in central vein (Figure 5e). Liver of rat in group (4) showing congestion in central vein and few fibrosis and inflammatory cells infiltration in portal area (Figure 5f). Liver of rat in group (5) showed dilatation of portal vein with collagen proliferation in portal area (Figure 5g). Figure 5h showed normal histological structure for liver of rats in group (6).

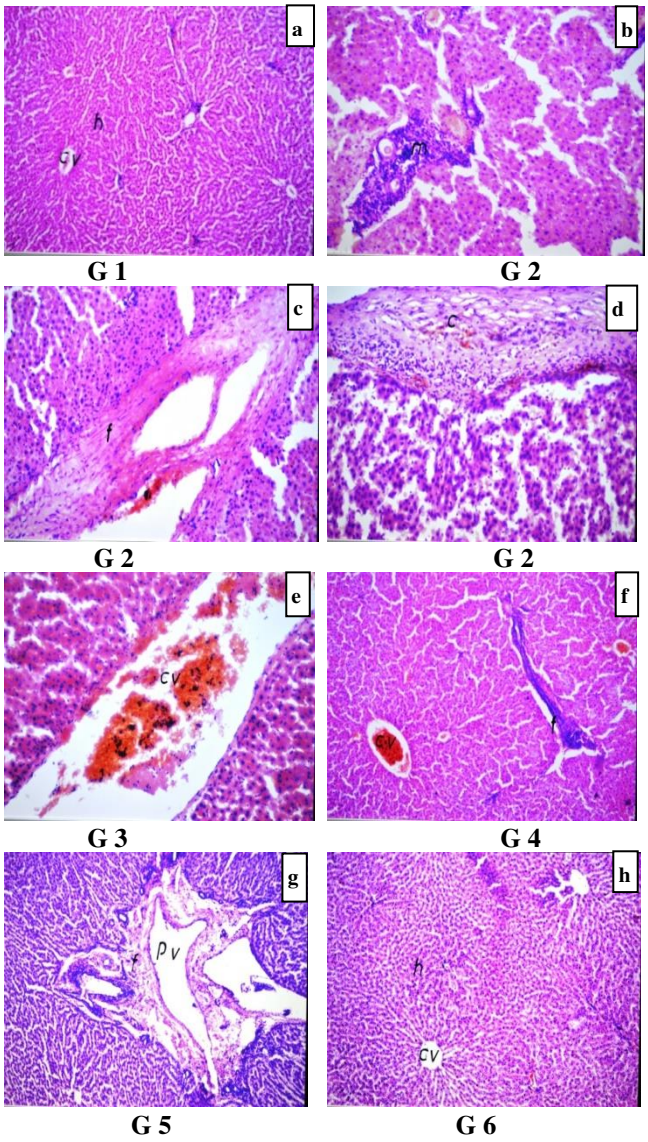


Figure 5: Hematoxylin and eosin- stained sections of rat liver; G1: normal control; G2: alloxan group; G3: treated with extract; G4: treated with moringinine; G5: treated with quercetin; G6: treated with chlorogenic acid; (cv): central vein; (h): hepatocytes; (m): inflammatory cells infiltration; (pv): portal vein; (f):fibrosis.

DISCUSSION

Cancer is the largest single cause of death in both men and women. Recently, resistance to anticancer drugs has been observed. Therefore, research and development of

more effective and less toxic drugs by the pharmaceutical industry has become necessary. Chemicals as well as biological agents that induce apoptosis have been reported to be promising interventions in the management of malignant cancer. Antiproliferative screening of models *in vitro* provide important preliminary data to help select plant extracts with potential antineoplastic properties for future study.

In recent decades *Moringa oleifera* leaves, flowers, gums, roots and seeds are widely used for many diseases including inflammation, cardiovascular and liver diseases, immune boosting agent, regulate blood sugar and cholesterol.[27] Taking into account the use in folk medicine of *Moringa oleifera* and its widespread claims of the medical effectiveness and the lack of experimental studies on its apoptotic activity, the present investigation was undertaken to evaluate the antiproliferation and apoptosis of the ethanolic extract of *M. oleifera* leaf on two human tumor cell lines.

It is well established that the compounds which exhibit IC50 in the range of 10–25 µg/ml are considered weak anticancer drugs. On the other hand, the compounds show IC50 values in the range between 5 and10 µg/ml are moderate antitumor agents, while those exhibit IC50 activity below 5µg/ml are considered strong antitumor agents.[23]

On comparing the IC50 values of the extract and the other three compounds, we have found promising and variable activities against the studied HepG2 and MCF-7 cell lines. The IC50 values for the quercetin and moringinine were occurred in the range 1.7–3.9 µg/ml, which they may be considered as strong antitumor drugs. The chlorogenic showed IC50 values corresponding to weak antitumor agents.

The therapeutic effects of *Moringa oleifera* may be due to the combination of various bioactive compounds. The high performance liquid chromatography analysis of *Moringa oleifera* extract indicated the presence of the many bioactive compounds such as kaempferol, quercetin, rutin, and gallic, chlorogenic, ellagic, and ferulic acids.[24]

Moringa oleifera provides a safe, cheap, and easy to handle source of alternative medicine. Moreover, the bioactive phenolic glycoside, 4-[(2′-O-acetyl-α-L-rhamnosyloxy) benzyl] isothiocyanate, of *M. oleifera* was found to decrease inducible nitric oxide synthase expression and inhibit cyclooxygenase-2, which shows its potential for anti-inflammatory and cancer chemoprevention activities.[25]

Sangkitikomol et al performed the HepG2 cells viability test and found that *Moringa oleifera* extract at the 2000-3000 mg/L concentration range significantly reduced the numbers of living cells ($P<0.05$) using the MTT assay.[26] Therefore, the toxic effect of *Moringa oleifera* extract at high doses may be due to its inhibitory or stimulatory actions via kinase signalling pathways, which are likely to affect cellular functions by altering the phosphorylation state of target molecules and by modulating gene expression.[27]

Other studies have indicated that lower concentrations of flavonoids (nanomolar level to low micromolar levels) could lead to antioxidant response element-mediated gene expression, including that of phase II detoxifying enzymes. In contrast, higher concentrations of flavonoids may sustain the activation of mitogen-activated protein kinases or stress-activated protein kinases, which could induce apoptosis and direct activation of the caspase cascade in the mitochondrial pathway by inhibiting survival signaling.[28,29] Several studies have described the adverse actions of flavonoids at the cellular level. For example, due to the toxic effects of flavonoids at high concentrations, DNA strand breaks are induced when using flavonoids such as quercetin and kaempferol.[30,31]

Also Berkovich et al examined the effect of *M. oleifera* aqueous leaf extract on the viability and cell cycle of cultured human pancreatic cancer cells, and evaluated its ability to modify the expression of key proteins of the NF-kB signaling pathway.[32] The author reported that *M. oleifera* leaf extract inhibits the NF-κB signaling pathway and increases the efficacy of chemotherapy in human pancreatic cancer cells.

Elevation of ALP activity in alloxan treated rats explains the liver tissue damage after being exposed to certain pharmacological agent such as alloxan. The level of total proteins was significantly reduced in these untreated rats; these results are in accordance with *Wilson and Islam.*[33] Administration of alloxan decreases serum protein levels due to increased non-enzymatic glycosylation of protein.[34]

Treatment with *M. oleifera* leaf extract significantly elevated serum total protein concentrations, which is possibly associated with a decreased affinity of albumin towards glucose.

The normalization of the two parameters seen in rats treated with the *M. oleifera* extract and it's activate ingredients (moringinine, quercetin and chlorogenic acid) indicated inhibition of liver cell injury and reduction of leakage of the enzymes into the blood. These results are in agreement with recent study, which revealed that *M. oleifera* leaf extracts reduced the toxicity due to elimination of the toxic products of acetaminophen in rats.[35]

Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthene, these are present in the *M. oleifera* and so responsible for this effect.[36,37]

The mechanism of protection of chlorogenic acid was dependent on the antioxidant activity of this acid to reduce the oxidative stress.[38]

Treatment with quercetin resulted in a significant improvement in liver function. Therefore, the antioxidant efficacy of quercetin may be due to its higher diffusion into the membranes allowing it to scavenge ROS at several sites through the lipid bilayer.[39] It can be also resulting from its pentahydroxyflavone structure allowing it to chelate metal ions via the orthodihydroxy phenolic structure and by scavenging lipid alkoxyl and peroxyl radicals.[40,41]

The antioxidant properties of the extract, chlorogenic acid and quercetin in alloxan rat model (and also antidiabetic effect) were confirmed in our early study.[13]

CONCLUSION

In conclusion, *M. oleifera* ethanolic leaf extract has anti-proliferative effect on human tumour lines (HepG2 and MCF-7); this effect is largely attributed to quercetin and moringinine, on the other hand chlorogenic acid is a potent hepatoprotective in alloxan- rat model. Further investigations in the areas of anti-carcinogenic effects of M. oleifera are advocated especially in vivo.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ali FT, Hassan NS, Abdrabou RR. Hepatoprotective and antiproliferative activity of moringinine, chlorogenic acid and quercetin. Int J Res Med Sci 2016;4:1147-53.