The Egyptian Journal of Hospital Medicine (Jul. 2015) Vol. 60, Page 336-346

Comparative Protective Effect of Moringa and Dandelion Extracts Against Hepatic Disorders and Oxidative Stress Associated with Prolonged Use of BrufenDrug in Rats

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ABSTRACT

Bachground: The nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently used medications worldwide for the treatment of a variety of common chronic and acute inflammatory conditions. The association between NSAIDs and liver disease is poorly documented. **Aim**: the current study was carried out to investigate the hepatic disorders associated with prolonged use of Brufen drug and evaluate the role of both moringa and dandelion extracts as hepatoprotective agents against these disorders. **Methods**: rats were divided into six groups (six rats/ each) as follow: group 1: rats did not receive any treatment and served as control; group 2 : rats orally administrated moringa extract (300mg/kg b.wt) daily for 12 weeks; group 3: rats orally administrated dandelion extract (300mg/kg b.wt) daily for 12 weeks ; group 4: rats orally administrated Brufen (18mg/kg b.wt) daily for 12 weeks;.group5: rats orally administrated moringa extract (300mg/kg b.wt) daily for one week alone then concomitant with Brufen (18mg/kg b.wt) for 11 weeks ;group 6: rats orally administrated dandelion extract (300mg/kg b.wt) daily for one week alone then concomitant with Brufen (18mg/kg b.wt) for 11 weeks.**Results:** the present results showed that the administration of Brufen led to significant increases in the levels of TL, TC, TG, LDL-C, ALT, AST, ALP, GGT, MDA and XO. While significant decreases in HDL-C, TP, ALP, GSH, TAC, SOD, CAT and GSH-Px, were recorded in Brufen treated rats group. On the other hand, the administration moringa or dandelion extracts succeeded to alleviate these abnormalities resulted from Brufen drug as indicated by the clear amelioration of occurred hepatic metabolic disorders, oxidative stress and histopathological changes in addition to improvement of the antioxidant status. **Conclusion**: it could be concluded that moringa or dandelion extracts have a remarkable role in management the hepatic disorders and oxidative stress associated with prolonged use of Brufen. Additionally it was recorded that moringa extract was more beneficial than dandelion extract in alleviating the occurred adverse effects of Brufen.

Keywords: Moringa, Dandelion, Hepatic disorders, Brufen drug**.**

Abbreviations:

ME ,moringa extract; DE, dandelion extract; B, Brufen; TL, total lipids; TC,totalcholesterol;TG,triglycrides;HDL-C,highdenisity lipoprotein cholesterol;LDL-C,lowdensity lipoprotein cholesterol; TP, total protein; Alb, albumin; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyltranspeptidase.; MDA, malondialdehyde; XO;xanthine oxidase GSH, reduced glutathione;TAC,total antioxidant capacity, SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; ROS, reactive oxygen species; NSAIDs, nonseroidal anti-inflamatory drugs

1. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently asked groups of pharmaceutical dealership all over the world**.** NSAIDs are pharmaceutical agents with various analgesic, anti-inflammatory and antipyretic characteristics. Chemically, NSAIDs are a different group and are not closely linked in terms of infrastructure; but, they have in common several therapeutic application and side effects. The most widely used drugs within NSAID are ibuprofen (IBP), diclofenac (DCF), acetylsalicylic acid (ASA), paracetamol and naproxen (NPX)**.** Brufen (ibuprofen) has effectual anti-inflammatory, analgesic and antipyretic properties. It has effective action on muscle pain and several other inflammatory diseases **[1].**Brufen acts by inhibiting the cyclooxygenase enzyme system, particularly COX-1 (constitutive) and COX-2 (induced at the site of inflammation). The cyclooxygenase are responsible for converting arachidonic acid to prostaglandins and thromboxanes, which are mediators, participated in various homeostatic

Received:8/1/2015
Accepted:2/2/2015
DOI : 10.12816/0013792

processes out the body**.** Mitochondrial dysfunction followed by acute hepatic necrosis sequent to acute or a chronic administration of Brufen. The declined activity of the antioxidant enzymes and disturbance of Ca^{2+} homeostasis result in loss of integrity of cell membrane **[2]**.However, mainly hepatic disorders are common unfavorable side effect subsequent acute and chronic administration of NSAIDs **[3]**. The beneficial effects of many medicinal plants may be due to the presence of antioxidative, antibacterial and antimicrobial components. Antioxidants such as flavonoids, phenolic acids and diterpenes can be used to treat the undesirable and harmful action of the free radicals **[4]**.Moringa*(Moringaoleifera)* is one of the most frequently distributed and naturalized among the species of family Moringacae and is called "Miracle tree" because of it has high medicinal properties. Its leaves are good source of natural antioxidants due to the presence of several constituents as flavonoids, phenolics ,ascorbic acid and carotenoids**.** Moreover, the leaves have antihypercholestorelemic effect treat diabetes mellitus, antihypertensive action, antitumor activities and anti-inflammatory agents **[5]**.Furthemore, dandelion (*Taraxacumofficinale)*of family Asteraceae, is used in rural population against human disease as hepatic and renal disorders **[6]** and several other diseases including, bronchitis, asthma, cough, GIT infection, inflammation and diuretic. The leaves are rich in fibers, iron, calcium and potassium. Dandelion is a good source of flavonoids, Polyphenols, alkaloids, glycosides, reducing sugars, saponins and tannins **[7]**.Therefore, the aim of this study was to compare the protective role of moringa and dandelion extracts against hepatic disorders and oxidative stress induced by prolonged use of Brufen drug.

2. Materials and methods

2.1. Chemicals

Brufen (B) was purchased from pharmaceuticals and chemical industries company, Cairo, Egypt. The drug was dissolved in distillated water and given orally at a dose of 18mg/kg bw, equivalent to the human therapeutic dose **[8].** All other chemicals used in the experiment were of analytical grade.

2.2. Plant materials

Moringa and danelion extracts

Packed clean dried leaves of moringa (*Moringaoleifera*) and dandelion (*Taraxacumofficinale*) were purchased from Metro market, Mansoura, Egypt.For each plant, 40g of the powdered leaves were soaked in 250 ml of ethanol (70%), shaken for 10 minutes then allowed to stay in refrigerator for 3 days at 4^{o}C. The mixtures were filtrated with WhatMan No 1 filter paper.The filtrates were separately concentrated using Rotary Evaporator, weighed and dissolved in distilled water to give the final concentration of 300 mg extract /kg bw. The chosen doses of moringa extract and dandelion extracts (300mg /kg b.w) were according the previous studies of **[9]** and **[10]** respectively.

2.3. Experimental animals

Thirty six healthy male albino rats *(Rattusrattus*), 8 weeks old, weighing 150-170g were used in this study. Rats housed in a stainless steel cages with automatically regulated temperature (22-25°C). They were kept under good ventilation and a photoperiod of 12 h light: 12 h darkness.The rats received water *ad libitum* and standard chow.

2.4. Experimental design

Rats were divided into six groups, six rats each and received their treatment daily for 12 weeks as follow: group 1: rats did not receive any treatment and served as control; group 2 : rats orally administrated moringa extract (300mg/kg b.wt) daily and for 12 weeks.; group 3: rats orally administrated dandelion extract (300mg/kg b.wt) daily for 12 weeks .; group 4 rats orally administrated Brufen (18mg/kg b.wt) daily for 12 weeks;.group5: rats orally administrated moringa extract (300mg/kg b.wt) daily for one week alone then concomitant with Brufen (18mg/kg b.wt) for 11 weeks ;group 6: rats orally administrated dandelion extract (300mg/kg b.wt) daily for one week alone then concomitant with Brufen (18mg/kg b.wt) for 11 weeks. follow: group 1 served as control; group 2was orally administrated moringa extract (300mg/kg b.w); group 3 were orally administrated dandelion extract (300mg/kg b.w) .group 4 were orally administrated Brufen (18mg/kg b.w).group5 was orally administrated moringa extract (300mg/kg b.w) daily for one week alone then concomitant with Brufen (18mg/kg b.w) for 11 wks.;group6 was orally administrated moringa extract (300mg/kg b.w) daily for one week alone then concomitant with Brufen (18mg/kg b.w) for 11 wks.

2.5. Blood collection and tissue homogenate

At the end of the experimental period (12 wks.) rats were fasted overnight and blood samples from each rat were collected from the eyes by retro-orbital puncture using blood capillary tubes. Blood samples from each rat were collected into clean centrifuge tubes, which were centrifuged at 860 Xg for 20 minutes for separation of sera. The sera were frozen at -20^{o}C for different biochemical analysis. The rats were sacrificed 24 h after the last treatment and

dissected, then the liver of each rat was removed ,weighed and homogenized in distilled water to form 10 %(w/v) homogenates. After labeling the samples, there were kept at -20^{o}C. Other samples of the liver tissue were stored in neutral formalin (10%) for histopathological studies

2.6. Parameters assay

The following biochemical parameters were determined in the serum and liver tissues: total lipids **[11]**, total cholesterol **[12],**Triglycerides **[13],** high-density lipoprotein cholesterol(HDL-C) **[14],** low density lipoprotein cholesterol (LDL-C) **[15],** total protein **[16],** albumin (Alb) **[17],** total bilirubin **[18],** alanine transaminase (ALT) and aspartate transaminase (AST) **[19],** alkaline phosphatase (ALP) **[20],**gamma-glutamyltranspeptidase (GGT) **[21].**Whereas the following parameters were estimated in the liver tissues: lipid peroxidation **[22],** xanthine oxidase (XO) **[23],** reduced glutathione content **[24],** total antioxidant capacity (TAC)**[25]** superoxide dismutase (SOD) **[26],** catalase (CAT) **[27],** glutathione peroxidase (GSH-PX) **[28].**

2.7. Histopathological Studies

The livers were removed from the animals and the tissues were fixed in 10% formalin for at least 24 h. Then, the paraffin sections were prepared (Automatic tissue processor, Autotechnique) and cut into 5 µm thick sections using a rotary microtom. The sections were then stained with Haematoxylin-Eosin dye followed by microscopic examination for any histopathological changes **[29].**

2.8. Statistical analysis

Results were expressed as means ± SE. Statistical significance was calculated using one-way analysis of variance (ANOVA) followed by Duncan′s multiple range tests **[30].** All the statistical analysis was carried out with the use of SPSS 15.00 software. Differences were considered significant at $P \leq 0.05$.

3. RESULTS

As shown in Table 1, the administration of Brufen drug resulted in a significant increase in serum TL, TC, TG, LDL-C, and bilirubin, as well as hepatic TL, TC, TG and decrease in HDL-C, TP and Alb. Also, as showed in Table 2, there is a significant increase in enzymes (ALT, AST, ALP and GGT) activity in both serum and liver in Brufen treated rats group compared to the control group. However, it was recorded a significant increase in MDA content and XO activity, at the same time, significant decrease in GSH, TAC, SOD, CAT and GSH-Px in Brufen treated rats (Table 3). Meanwhile, pre-administration of moringa or dandelion extract before Brufen administration succeeded to ameliorate the liver oxidative stress markers and biochemical alterations in addition to improvement the antioxidant status (Tables 1–3). Meanwhile, a marked improvement in the above-mentioned parameters was observed in rats administered moringa indicating that moringa has the best effect than dandelion.

4. DISCUSSION

In this study, the administration of Brufen for 12 weeks led to negative results in all tested biochemical parameters that is an indicator for hepatic disorders. However there are improvements by administration of moringa or dandelion extract before Brufen.Brufen (ibuprofen) has a vital antipyretic and analgesic role**.** It is metabolized to extractable glucuronide and sulphate conjugates in the liver.It is known to be the cause of hepatic disorders in human and experimental animals at high doses. Hepatic disorders by Brufen may be due to the formation of toxic metabolites. Prolonged use of Brufen resulted in dysfunction of mitochondria followed by acute necrosis of hepatic cells. All these events culminate in morphological and functional changes resulted in loss of cell membranes integrity which is seen from high levels of serum hepatic enzymes **[31]**. Damage of hepatocytes may be due to disturbance of Ca^{2+} homeostasis and the reduced activity of the antioxidant enzymes**.** Chronic administration of Brufen result in unspecified increment in permeability of the plasma membrane, mitochondrial membrane and smooth endoplasmic reticulum membranes resulted in disorders of calcium homeostasis by rise intracellular calcium. Disabled calcium homeostasis may be attributed to reduction of available NADPH, a cofactor required by calcium pump. Disturbance of calcium homeostasis lead to the activation of many membrane damaging enzymes like ATPases, phospholipases, endonucleases and proteases, disruption of mitochondrial metabolism and ATP synthesis and damage of microfilaments used to support cell structure **[32].**

Moreover, the production of oxidative stress is generation by peroxidase-catalyzed reaction mitochondrial injury (uncoupling of oxidative phosphorylation and decrease ATP synthesis**) [33]** and immune-mediated mechanisms (have been also suggested to play a vital role in hepatic disorders caused by Brufen. In addition to the generation of reactive metabolites, Brufen hepatic disorders involved injury of mitochondria. So this damage may be due to the oxidative stress followed by mitochondrial permeability transition (MPT). MPT led to leakage of cytochrome c and other proteins leading to apoptosis **[34]**. The increased

deposition of lipid droplets (microvesicular steatosis) observed in hepatocytes of animals receiving high dose of NSAID may be attributed it to dysfunction of mitochondria and altered oxidative phosphorylation and fatty β oxidation. Increased concentrations of intracellular fatty acids may be directly toxic to hepatocytes or lead to oxidative stress **[35].**Also, mitochondrial fatty acid β-oxidation became impaired causing steatosis that leads to lipid peroxidation, whose reactive products malonaldehyde (MDA) and 4-hydroxy-nonenal (HNE) damage the respiratory chain and mtDNA and stimulate collagen synthesis by Ito cells **[36].**

On the other hand, reactive oxygen species (ROS) play an important role in hepatic disorders, by activation of Kupffer cells (stellate macrophages) by damaged hepatocytes membrane, metabolites of toxic agents and infiltrating inflammatory cells. The activated Kupffer cells release a number of agents such as transforming growth factor-α (TGF-α), platelet-derived growth factor (PDGF), and tumor necrosis factor-α (TNF-α) and ROS. These factors act on the hepatic stellate cells (HSC, fat-storing cells, or Ito cells), that are localized in the parasinusoidal space undergo morphological transition to myofibroblast-like cells with subsequent excessive production of extracellular matrix (ECM) components **[37].**

In the present study, the observed hyperlipidemia due to Brufen administration was manifested byincrease total lipids, total cholesterol, triglycerides, LDL-C and decrease HDL-C. The observed hyperlipidemia may be due to the reduction of lipoprotein lipase and increased hepatic synthesis**.**The rise in serum lipids might reflect the impairment of hepatocytes to metabolize lipids or lipid peroxidation **[38].** In addition, lipid peroxidationis involved in hepatic damage leading to cell death due to oxidative stress which is caused by an alteration in the intracellular prooxidant to antioxidant ratio in favor of prooxidants. Lipid peroxy radicals resulted in increased permeability of cell membrane, decreased fluidity of cell membrane, inactivation of membrane proteins and loss of polarity of mitochondrial membranes**.**

Moreover, during the oxidative stress, the generation of free radicals can have several consequences. Free radicals can react with and cause damage to DNA, proteins and lipids**.**These results also may be attributed toBrufen caused peroxidative degeneration in the adipose tissue resulting in the fatty change and infiltration of the hepatocytes **[2].**

Moreover, Brufen caused changes in the architecture of the hepatocytes, cell permeability and to create ionic imbalance resulting in increased intracellular calcium concentration. Consequently, mitochondrial activity was inhibited; leading to the death of hepatocytes **[39].**The observed hepatic disorders due to Brufen administration was manifested by marked increase in liver enzymes activities and bilirubin content companied by a decrease in albumin and total protein content. The disturbance of ALP and bilirubin may be due to bile excretion which is inhibited by hepatotoxicity which leads to increase of the normal values due to the body's inability to excrete it through bile due to the obstruction or congestion of the biliary tract, which may occur within the liver, the ducts leading from the liver to the gallbladder, or the duct leading from the gallbladder through the pancreas that empty into the duodenum **[40].** In addition, the markedly elevated bilirubin level may be a result of the liver cells is damaged; they may not be able to excrete bilirubin in the normal way, causing a build-up of bilirubin in the blood and extracellular fluid. Also the increase of serum bilirubin showed the severity of jaundice. Increased levels of bilirubin may also result due to decreased hepatic clearance and lead to jaundice and other hepatotoxicity disorders **[41]**. The significant decline in total proteins content which observed in rats administrated with Brufen that induced hepatic disorders may be attributed to an increase in amino acid deamination and significant fall in protein synthesis **[42]** which could be due to the peroxidative damage of liver**.** In addition, Brufen was also found to be most active in impairing albumin synthesis **[43].**

The possible explanation of observed increase in the liver marker enzymes (ALT,AST and GGT) might reflect cell rupture ,a major permeability, cellular leakage , loss of functional integrity of the cell membrane and the release of these enzymes from the damaged liver parenchymal cells. In addition, significant increase in the ALP which may be attributing to elevated biliary pressure **[44]**.Also, the elevation of liver enzymes activities by Brufen might be due to the intracellular accumulation of Ca^{2+}, which results in activation of phosphofructokinase and anaerobic glycolysis. Loss of Ca^{2+} homeostasis as a result of oxidative damage and the increase in intracellular Ca^{2+} has been reported to a late and perhaps irreversible final stage in the process of cell death by Brufen**[45].**The current results indicated that administration of Brufen increase oxidative stress and decrease

antioxidant enzymes. Also, oral administration of Brufenwasaccompanied by a significant increase in lipid peroxidation (LP) levels and xanthine oxidase (XO) activity consequently, it is concluded that the active oxygen species, derived from XO play an important role in the pathogenesis caused by Brufen**[46].** Lipid peroxidation of hepatic cell membrane is one of the principle causes of hepatic disorders induced by Brufen. This is because lipid peroxidation is viewed as a complicated biochemical reaction involving free radicals, metal ions, oxygen and a host of many different factors in the biological system. Also, lipids have been recognized as important molecules in signal transduction **[47]**. The efficacy of any liver therapeutic drug depends on its capacity of either reducing the harmful effect or restoring the normal hepatic physiology that has been made disorders by hepatotoxicants**[48]**. Malondialdehyde (MDA) is one of the important end products of polyunsaturated fatty acid peroxidation and its level act as clear indicator of lipid peroxidation in tissues especially hepatic cells **[49]**. MDA was increased in hepatocytes demonstrated in the present study after administration of Brufen could be expected owing to the decrease in hepatic GSH content and GPx activity. This is a clear indicator for increase the level of lipid peroxidation, This disturbance can be explained as hepatic tissue contains a high content of polyunsaturated fatty acids, which are sensitive to peroxidative damage **[50]**

Moreover**, t**he present results concluded that there were a significant depletion in hepatic GSH, TAC, SOD,CAT, GSH-Px and increase in XO and MDA in the Brufen treated rats group. Antioxidant enzymes (SOD, CAT, and GPX) play a major role in the intracellular defense against oxygen radical damage **[51]**. The depletion of GSH level in the Brufen rats group might be attributed to its utilization by the extremely generated quantity of free radicals and ROS in the liver cells leading to hepatic disorders. Decreased GSH levels leads to significant increase in oxidative stress .Decline of glutathione with concomitant a significant increases in lipid peroxide levels were clear indication of the vital role of glutathione during oxidative stress. These results may be attributing to their prolonged utilization to scavenge the products of lipid peroxidation **[52]**. SOD and CAT are the first line of defense against Brufen induced hepatic oxidative damage. SOD is the primary step of the defense mechanism in the antioxidant system against oxidative stress by catalyzing the dismutation of superoxide radicals (O2−) into molecular oxygen (O2) and hydrogen peroxide (H2O2). H2O2 is neutralized by the action of catalase **[53].**Catalase (CAT) which is another important antioxidant enzyme that decomposes hydrogen peroxide and protects tissue from reactive hydroxyl radicals is widely distributed in all animal tissues. Administration of Brufen alone significantly decreased SOD and CAT activity, indicating oxidative stress **[54].** A significant depletion in SOD, CAT activities may be due to the increase superoxide radical formation leading to oxidative stress in the hepatic cells and utilization of SOD, CAT enzymes during reactive metabolites detoxification **[55].** In other hand, the present histopathological study suggested that the administration of Brufen revealed considerable number of damaged hepatocytes that have lost their characteristic appearance, with manifestations of hydropic degeneration, appearance of pyknotic nuclei, fatty infiltrations, inflammatory leukocyte infiltrations, severe congestion of portal vein and fragmented endothelium.These changes may be due to the reactive oxygen species and lipid peroxidation play an important role in hepatocytes disorders **[56].**

On the other hand, medicinal plants with antioxidant properties resulted in recovery of damaged cells. The present administration of moringa or dandelion before Brufen can be improved all the occurred liver function and structure alterations through their hepatoprotective effects and antioxidants properties. Moringa extract has got an intense hypolipidemic activity, this finding may be attributed to its potential to control the mechanisms involved in disposal of lipids from the body **[57].** Moreover, administration of moringa extract before Brufen improved the liver functions that manifested by marked decrease in liver enzymes and bilirubin and companied by increase in albumin and total protein. These improvements were a clear indicator about hepatoprotective effects of moringa. Also, the improvement in liver functions may be due to moringa extracts which has a potential components with therapeutic properties against hepatotoxicity induced by Brufen in rats. The hepatoprotective effects of moringa extracts are probably due to enhanced antioxidant enzymes as well as inhibition of lipid peroxidation **[58].** Furthermore , improvement of these enzymes may be due to moringa extract reduced the damage accelerated regeneration of parenchymal cells, mitochondria and lysosomes, thus protecting against lysosomal integrity and cell membrane fragility, and therefore decreasing the leakage of liver

enzymes into the blood stream **[59].** In addition, amelioration of serum total bilirubin level during preadministration of moringa extract is a good indicator of the amelioration of hepatocytes functions **[60].** The markedly declined in the total protein and albumin levels in serum by oral administration of Brufen causes hepatic disorders by induction of lipid peroxidation and inhibits the synthesis of protein **[61].** The improvement of proteins by administration of moringa may attributed to inhibition of lipid peroxidation and scavenge of the free radicals **[62].**

Also, pre administration of moringa extract before Brufen reduced MDA, XO and increase GSH, TAC, SOD, CAT and GSH-Px. These findings may be attributed to moringa extract contains more than eight thousand antioxidant components, ranging from simple phenol to complex materials as tannins.Phenolic compounds have profound antioxidant properties. Moreover, moinga extract contains poly phenols, flavonoids β-sitosterolkaempferol and quercetin which have hydroxyl groups. The hydroxyl group, because of its resonance property, easily donates e− to free radicals and effectively neutralizes them. Also, the presence of a hydroxyl group rises its antioxidant potential through inter molecular hydrogen bonding involving the -SH group of non-protein thiols and enzymes leading to the renovation of the antioxidant system against oxidative stress in hepatic cells **[63].** Also, special phenolic compounds may induce production of antioxidant enzymes.β-Carotene from moringa leaves has shown significant hepatoprotective effects and is efficiently converted into vitamin A in the body **[59].** The antioxidative defense system include enzymatic and non-enzymatic antioxidants playing a vital role in the consolidation of physiological levels of O_2 and H_2O_2 and eliminating the peroxides generated from acute and chronic exposure to drugs**.** Also, moringa extracts have therapeutic properties which may be attributed to presence of bioactive compounds and renovation of the GSH level. These results were proportionate with previous findings on hepatoprotective nature of moringa extracts **[64].** Moreover, liver section of the rat treated with Brufen supplemented with moringa extract demonstrated restoration of normal arrangement of hepatocytes, this might be due to lower fat accumulation and regeneration of the antioxidant defense system in the hepatic cells through the antioxidant and hepatoprotective nature of moringa leaves **[63].**

On the other side pre administration of dandelion extract before Brufen also improved lipid profile liver enzymes, bilirubin, total protein and albumin. These results may be due to the profound hypolipidemic and antioxidant effects**.** This amelioration may be attributing to the bioactive compounds (phytochemicals) in the dandelion extract that minimized the adverse effects and recovered the damaged liver **[6].** A decrease in bilirubin may be explained as the presence of sesquiterpene in leaves of dandelion, increase bile production in the gallbladder **[65]**.Also,this improvement may be due to dandelion extract reduced damage of the liver cells with subsequent acceleration of parenchymal cells regeneration, thus protecting against membrane fragility consequently, and minimizing the leakage of liver enzymes into the blood circulation and management the lipid metabolism **[66].** These findings may be also due todandelion extract contain lipotropic substance which can improve functionally of liver cells **[67].** Also, dandelion is important source of cichoric acid, luteolin ,luteolin-7-Oglucoside , flavonoid, alkaloids, steroids, and high content of polyphenol with potential application as radical scavengers (ROS) , play a vital role in controlling oxidation and prevent DNA from ROS-induced damage as evidenced by the observedinhibition of MDA as a good marker for lipid peroxidation and oxidative stress **[68],[69].** Moreover, the observed improvement of the liver section of the rat treated with Brufen supplemented with dandelion may be due to its beneficial effect and antioxidant properties resulted in recovery of damaged cells **[66].**

5. Conclusion

The use of natural products is increasing day by day, due to their effective therapeutic action and lack of side effects. The obtained data strongly suggested the efficacy of moringa or dandelion extracts supplementation as good hepatoprotective agents against the oxidative stress and hepatic disorders induced by Brufen administration. This achieved by the greatly positive effects on membrane stabilizing by mechanisms that include up-regulation of the antioxidant defense system , modulate oxidative stress and improvement of lipid metabolism through their antioxidant properties and ability for scavenging free radicalsthat responsible for hepatocytes damage. Additionally morenga is more effective than dandelion. Fractionation guided evaluation could help in the development of ideal anticancer in the near future.

6. Acknowledgments

The authors of this manuscript express their deepest gratitude and appreciation to **Dr. Abdfattah El beltagy Mohamed**, lecturer of Comparative Anatomy and Embryology, Zoology Department, Faculty of Science, Damanhour University, Damanhur, Egypt for his financial assistance in histopathological examination in the present work.

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Table 1: Serum and hepatic biochemical parameters in control and different treated rat groups.

Parameters		Animal groups					
		C	ME	DE	B	ME+B	DE+B
Serum	TL (mg/dl)	426.67 ±8.91[a]	419.33 ±5.43[a]	423.33 ±9.46[a]	624.83 ±7.70[b]	435.00 ±6.58[a]	513.33 ±4.41[c]
	TC (mg/dl)	102.92 ±0.58[a]	100.47 ±0.78[a]	101.67 ±2.08[a]	132.00 ±1.63[c]	107.00 ±2.42[a]	130.92 ±1.92[c]
	TG (mg/dl)	95.67 ±2.14[a]	94.95 ±1.19[a]	95.53 ±2.12[a]	126.84 ±1.27[b]	73.22 ±2.47[c]	97.38 ±1.58[a]
	HDLC (mg/dl)	50.25 ±0.70[a]	51.92 ±0.58[a]	50.30 ±0.56[a]	23.38 ±0.73[b]	41.08 ±0.58[c]	35.33 ±1.12[d]
	LDL-C (mg/dl)	33.53 ±0.78[a]	30.82 ±0.69[a]	33.02 ±1.89[a]	83.25 ±2.25[b]	50.03 ±1.69[c]	76.21 ±2.34[d]
	TP (g/dl)	10.29 ±0.22[a]	10.32 ±0.22[a]	10.30 ±0.26[a]	7.24 ±0.12[b]	9.33 ±0.10[c]	8.17 ±0.24[d]
	albumin (g/dl)	3.54 ±0.02[a]	3.56 ±0.06[a]	3.55 ±0.04[a]	3.29 ±0.05[b]	3.53 ±0.04[a]	3.50 ±0.04[a]
	bilirubin (mg/dl)	0.53 ±0.01[a]	0.51 ±0.02[a]	0.52 ±0.01[a]	1.01 ±0.05[b]	0.55 ±0.01[a]	0.67 ±0.01[c]
Liver	TL (mg/g)	1925.00 7.64[a]	1881.70 5.58[a]	1921.70 10.22[a]	2137.50 35.21[b]	1929.20 7.68[a]	2101.80 24.91[c]
	TC (mg/g)	114.00 ±1.06[a]	110.33 ±1.99[a]	112.67 ±1.71[a]	127.17 ±1.14[b]	103.17 ±2.21[c]	118.33 ±1.89[a]
	TG (mg/g)	346.17 ±7.23[a]	339.33 ±2.82[a]	341.92 ±6.46[a]	404.33 ±4.63[b]	363.50 ±1.61[c]	378.67 ±3.09[d]
	TP(g/g)	5.77 ±0.04[a]	5.80 ±0.01[a]	5.78 ±0.02[a]	4.11 ±0.04[b]	4.80 ±0.03[c]	4.45 ±0.04[d]

Results were presented as means ± SE (n=6 for each group).Letters (a-d) express the significant change at $p \leq 0.05$, Similar letters (non-significant), Different letters (significant).

C: control ME: moringa extract DE: dandelion extract B: brufen

Table 2: Serum and hepatic enzymes activity in control and different treated rat groups.

Parameters		Animal groups					
		C	ME	DE	B	ME+B	DE+B
Serum	ALT (1U/L)	27.58 ±0.62 [a]	26.90 ±0.73 [b]	27.50 ±0.68 [a]	50.50 ±0.76 [b]	32.50 ±0.76 [c]	45.50 ±0.76 [d]
	AST (1U/L)	34.00 ±1.06 [a]	32.67 ±0.88 [a]	33.67 ±0.42 [a]	50.50 ±0.76 [b]	38.17 ±1.08 [c]	46.50 ±0.76 [d]
	ALP (1U/L)	127.67 ±2.50 [a]	125.00 ±3.37 [a]	126.50 ±0.76 [a]	166.33 ±2.17 [b]	131.50 ±0.76 [a]	153.00 ±0.53 [c]
	GGT(1U/L)	22.35 ±0.47 [a]	22.00 ±0.34 [a]	22.30 ±0.53 [a]	26.95 ±0.15 [b]	23.56 ±0.20 [c]	25.62 ±0.21 [d]
Liver	ALT (1U/g)	52.58 ±0.54 [a]	50.67 ±0.44 [a]	51.96 ±0.29 [a]	82.50 ±0.48 [b]	54.50 ±0.76 [a]	69.67 ±0.88 [c]
	AST(1U/g)	71.67 ±0.44 [a]	70.00 ±0.53 [a]	70.33 ±0.44 [a]	81.83 ±0.53 [b]	61.83 ±0.53 [c]	78.25 ±0.67 [d]
	ALP (1U/g)	15.08 ±0.58 [a]	14.59 ±0.58 [a]	15.00 ±0.53 [a]	32.15 ±0.61 [b]	18.25 ±0.38 [c]	23.33 ±0.44 [d]
	GGT (1U/g)	23.96 ±0.27 [a]	23.00 ±0.50 [a]	23.50 ±0.21 [a]	28.76 ±0.47 [b]	25.08 ±0.34 [a]	25.84 ±0.18 [a]

Results were presented as means ± SE (n=6 for each group).Letters (a-d) express the significant change at $p \leq 0.05$ Similar letters (non-significant), Different letters (significant).
C: control ME: moringa extract DE: dandelion extract B: brufen

Table 3: Liver oxidative stress and antioxidant biomarkers in control and different treated rat groups.

Parameters	Animal groups					
	C	ME	DE	B	ME+B	DE+B
MDA(nmol/g)	799.99 ±28.77 [a]	790.00 ±28.66 [a]	795.00 ±27.70 [a]	1126.08 ±28.77[b]	800.25 ±25.65 [a]	841.64 ±24.76 [a]
XO (µmole/h/g)	1.47 ±0.09 [a]	1.43 ±0.03 [a]	1.45 ±0.05 [a]	3.62 ±0.09 [b]	2.25 ±0.04 [c]	3.14 ±0.02 [d]
GSH (mmol/g)	4.32 ±0.13 [a]	4.36 ±0.28 [a]	4.35 ±0.21[a]	3.30 ±0.07 [b]	4.31 ±0.06 [a]	4.30 ±0.23 [a]
TAC(mM/g)	1.45 ±0.02 [a]	1.47 ±0.02 [a]	1.46 ±0.01 [a]	1.34 ±0.02 [b]	1.44 ±0.01 [a]	1.43 ±0.02 [a]
SOD (U/g)	167.50 ±2.08[a]	168.00 ±2.02[a]	168.67 ±2.23[a]	110 ±2.93[b]	134.00 ±1.77[c]	119.17 ±2.30[d]
CAT(U/g)	192.67 ±1.86 [a]	195.00 ±1.15 [a]	193.67 ±2.60 [a]	134.50 ±0.76 [b]	184.00 ±1.06 [c]	164.83 ±1.19 [d]
GSH-Px(U/g)	749.27 ±5.99 [a]	759.18 ±1.16 [a]	750.39 ±6.27 [a]	637.06 ±7.26 [b]	745.18 ±5.83 [a]	700.15 ±2.75 [a]

Results were presented as means ± SE (n=6 for each group).Letters (a-d) express the significant change at $p \leq 0.05$ Similar letters (non-significant), Different letters (significant).
C: control ME: moringa extract DE: dandelion extract B: brufen

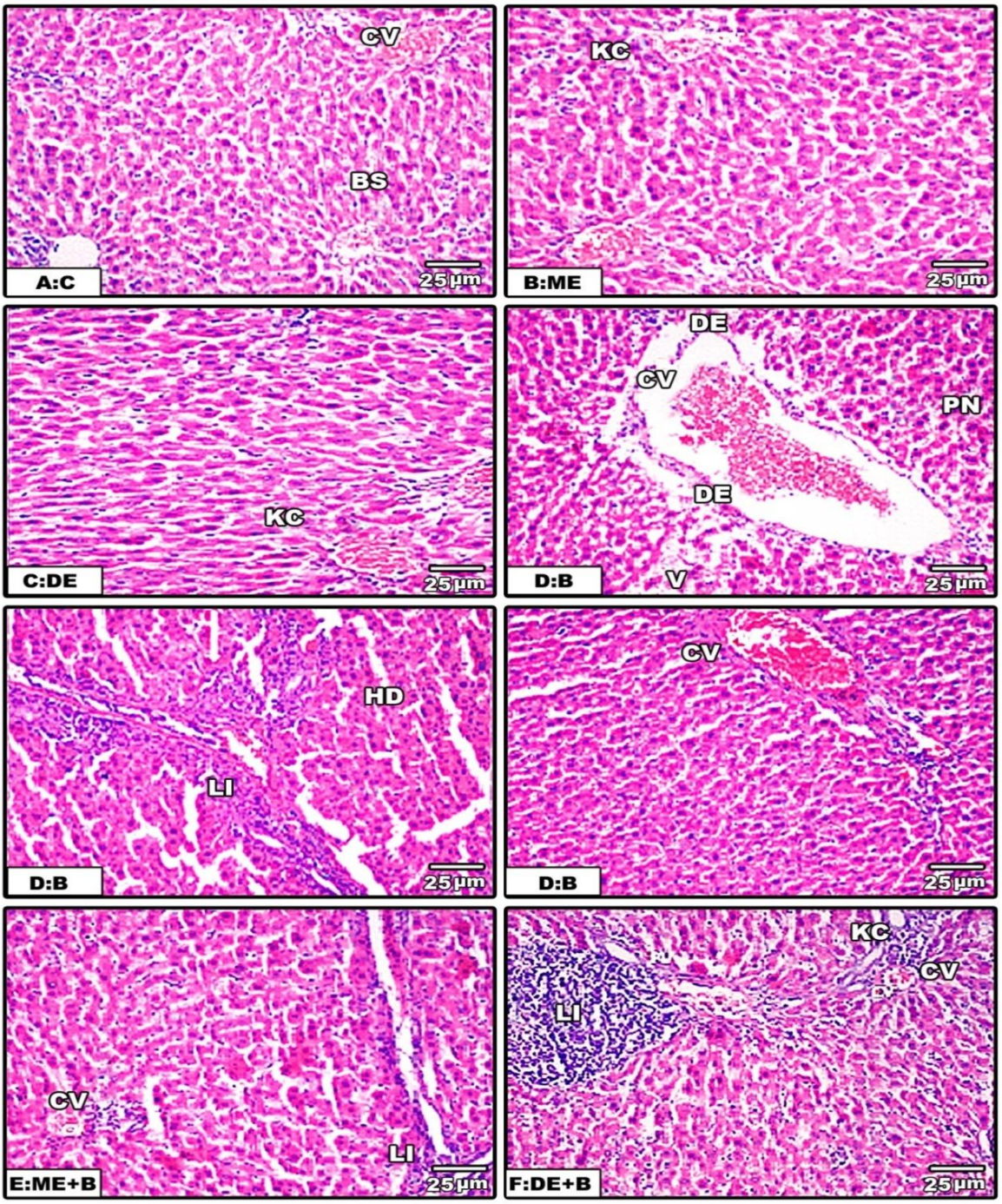

Plate 1, Figs, (A-F): Photomicrographs for liver sections stained with hematoxylin and eosin (H&E original magnification X400) A-C: Liver sections of control (A), ME treated (B) and dandelion extract received rats showing normal histological appearance of the liver, including central vein (CV), blood sinusoids (BS), hepatic cells (HC), kupffer cell (KC) and centrally located nuclei. D: Section of rat liver treated with Brufen revealed considerable number of damaged HC that have lost their characteristic appearance, with manifestations of hydropic degeneration (HD), appearance of pyknotic nuclei (PN), fatty infiltrations (FD), inflammatory leukocyte infiltrations (Li), severe congestion of portal vein and fragmented endothelium. E: Liver section of the rat treated with Brufen supplemented with ME demonstrated restoration of normal arrangement of hepatocytes, although dilatation in blood sinusoids (DBS) and cytoplasmic vacuoles (V) were observed. F: Liver section of the rat treated with Brufen supplemented with DE extract showing improvement in reconstruction of liver strands in spite of the dense inflammation in portal area still found