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RESEARCH ARTICLE

POTENTIAL ROLE OF MIMUSOPS LARIFOLIA BUTANOLIC EXTRACT AS AN ANTIOXIDANT AND ANTI-INFLAMMATORY AGENT AGAINST OXIDATIVE STRESS INDUCED IN OBESE RAT

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ABSTRACT

Mimusops Larifolia Leaves butanolic extract contains many phenolic compounds with high antioxidant activity which may have useful health properties including flavonoids, triterpenes, saponins, and amyrins. Oxidative stress is an imbalance between free radical production and the antioxidant defence system which could lead to lipid, protein, and /or DNA alterations. For the present study the strong antioxidant activity of (M. Bu. E) on some blood and serum parameters of male rats exposed to high-fat diet (HFD) -induced oxidative stress were investigated . Sixty male albino rats weighting 150- 200 g. were used. The rats were divided into six equal groups. 1) Control Normal group: provided only with a constant supply of standard ration. 2) Mimusops laurifolia (single dose) Group : provided with a constant supply of standard pellet diet, along with administration of M. Bu. E at (75.83 mg/kg b.wt.) orally, once daily for 8 weeks. 3) Mimusops laurifolia (double dose) Group : provided with a constant supply of standard pellet diet, along with M. Bu. E at (151.66 mg/kg b.wt.), once daily for 8 weeks. 4) HFD Stressed group : fed on high fat diet daily for 8 weeks; for induction of oxidative stress. 5) HFD + M. laurifolia (Single dose) Group: fed on high fat diet daily for 8 weeks; along with M. Bu. E at 80 mg/kg b.wt. orally and daily for 8 weeks. 6) HFD + M. laurifolia
(double dose) Group: fed on high fat diet daily for 8 weeks; along with M. Bu. E at 160 mg/kg b.wt. orally and daily for 8 weeks. Serium and Blood samples were collected from all animals groups, after 4 and 8 weeks from the oncet of experiment. The obtained results revealed that, HFD supplementation exhibited a significant decrease in the levels of SOD, GPx and Nitric oxide whereas it exhibited a significant increase in L-MDA, IL-6, CRP, levels. On contrast, supplementation of M. laurifolia to stressed rats yields a significant reverse estimation of the previously mentioned parameters. The present article revealed the potential pharmacological and phytpchemical effects of Mimusops Larifolia plant as a natural antioxidant and a powerful anti-inflammatory agent against harmful effects of oxidative stress induced by HFD and draw attention for further researches so as to work on untouched pharmacological properties.

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INTRODUCTION

Obesity is a chronic disease of multifactorial origin that develops from interaction of social, behavioral, psychological, metabolic, cellular, and molecular factors **(Kaufer et al., 2001)**. It is the condition under which adipose tissue is increased and results in excessive fat accumulation. Obesity is associated with atherosclerotic and cardiovascular diseases when body mass index (BMI) > 30 **(Sikaris, 2004).**

Oxygen free radicals can be easily generated by oxidation of membrane lipids to produce membrane peroxidation and malondialdehyde (MDA) formation, which increase membrane permeability, and inactivate membrane transporters by forming intra and intermolecular cross links representing an immediate risk to cell viability **(Rajguru et al., 1993) .**

Oxidative stress (OS), results from increased production of free radicals and reactive oxygen species (ROS) and /or a decrease in antioxidant defense, causing severe damage to biologic macromolecules resulting in protein fragmentation, oxidation of nucleic acids and dysregulation of normal metabolism and physiology **(Toyokuni, 1999).**

To minimize free radical damage, there is a complex antioxidant defense system, which prevent the organism from the harmful effects of free radicals by scavenging or inhibiting their formation **(Metin et al., 2002) .** Cells maintain their vital functions against oxidative

damage with the help of a system that involves glutathione peroxidase (GSH-Px), superoxide dismutase(SOD), catalase, glutathione reductase, some trace elements and vitamins A, E and C **(Aaseth et al., 1986).**

Lipid-rich diets are capable of generating ROS because they can alter oxygen metabolism. Upon the increase of adipose tissue, the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), were found to be significantly diminished. Finally, high ROS production and the decrease in antioxidant capacity leads to a reduction in the bioavailability of vasodilators, particularly nitric oxide (NO), and an increase in atherosclerotic disease **(Fernández et al., 2011)**.

Excessive fat accumulation can cause cellular damage due to pressure effect from fat cells (i.e., non alcoholic steatohepatitis). Cellular damage in turn leads to high production of cytokines such as TNF-α, IL_6 which generates ROS in the tissues, and increases the lipid peroxidation rate **(Khan et al., 2006)**. Visceral fat is a highly active tissue from the metabolic point of view. and is more susceptible to lipolysis than subcutaneous adipose tissue and is associated with higher production of plasminogen activator inhibitor-1 (PAI-1), IL-6, and CRP **(You et al., 2008).**

Nitric oxide (NO) is an important anti-atherogenic agent and act as a regulator of cardiovascular, neuromuscular, neurological, genitourinary, gastrointestinal, and renal functions. Inhibition of nitric oxide synthase (INO) by excessive free fatty acids reduce NO production and increase insulin secretion **(Lee et al., 1997) .** An increase in the production of superoxide free radical diminishes the availability of NO and cause vasoconstriction in the vasculature of the liver **(Dobrian et al., 2003).**

Mimusops laurifolia (Forssk.), a plant Species belonging to the genus Mimusops, are widely distributed in the Arabian Peninsula and are the most important plant species in the Arabian region for its fascinating ethno-botanical history. **(Hall et al., 2010).**

Mimusops elengi are reported to be used in traditional medicine in India. **(Shah et al., 2003).**

All parts of plant such as leaf, root, fruit, seed, bark, flower were reported for treatment of various human ailments in traditional system of medicine like antimicrobial, antifungal, antioxidant and free radical scavenging, anti-inflammatory analgesic, antipyretic, antiurolithiatic, cytotoxic, diuretic, neuroprotective, anti-amnesic, cognitive enhancing, antihyperglycemic, antihyperlipidemic, hypotensive, antiulcer, anthelmintic, antitumor, wound healing, larvicidal activities **(Seema- Khaleequr et al., 2017).** A number of bioactive molecules including flavonoids, phenoic compounds, alkaloids, and terpenoids previously reported for their cancer properties were identified from this plant that may be responsible for its pharmacological activities **(Gami et al., 2012).**

Mimusops laurifolia seeds are known to produce nine kinds of saponins **(Eskander et al., 2006).**

(Lee et al., 2000) reported that saponins possess anti-lipid peroxidation activity to protect the vascular endothelium, and to prevent diabetic complications. A large number of research found that saponins is a traditionally natural surface-active glycosides that have a variety of biological active fuctions, and played a positive role in increasing antioxidant capacity, anti-tumor, reduce cholesterol, improve immunity and other useful biological functions **(Chen et al., 2014)**. Crude methanolic extract of the leaves of mimusops elingi exhibited statistically significant antioxidant activity by using DPPH (1, 1-diphenyl-2-picrylhydrazyl) scavenging assay and Nitric oxide scavenging test **(Purnima et al., 2010)**.

The extract showed significant activities in all antioxidant assays compared to the reference antioxidant ascorbic acid in a dose dependent manner **(Saha et al., 2008)**. Total phenolic content was found to be 97.3 µg/mg of extract. The maximum membrane stabilization of M. elengi L was found to be (73.85±0.80 %) at a dose of 1000 µg/0.5 ml and that of protein denaturation was found to be 86.23 % at a dose of 250 µg/ml with regards to standards in the anti-inflammatory activity. **(Kar et al., 2012)**.

Kar et al., assessed the antioxidant and in vitro anti-inflammatory activities of alcoholic extract of *Mimusops elengi* leaves. The leave extract exhibited dose dependent free radical scavenging property in peroxynitrite, superoxide and hypochlorous acid models and the IC50 value were found to be (205.53 ±2.30), (60.5±2.3), (202.4±5.3) µg/mL respectively. The ethanol extract of bark was assessed for antiinflammatory, analgesic and activities in animals.

The ethanol extract of *Mimusops elengi* bark significantly inhibited the carrageenan-induced paw oedema at 3rd and 4th h and in cotton pellet model it reduced the transudative weight and little extent of granuloma weight **(Purnima et al., 2010)**. Petroleum ether, chloroform, and alcohol extracts of bark were evaluated for in-vivo antioxidant activity, which includes lipid peroxidation (MDA), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). It produced significant decreased in MDA and increased in GSH, SOD and CAT. The alcohol extract shows more potent antioxidant activity than petroleum ether and chloroform extract **(Ashok et al., 2010).**

The present study aimed to investigate the biochemical role of *M. Larifolia* Leaves extract on some antioxidant and anti-inflammatory parameters of blood and serum male rats exposed to HFD -induced oxidative stress .

MARTIALS AND METHODS

Ration and additives :

Animals were fed on ration throughout the acclimatization period of the experiment in the form of pelleted concentrated ration shown in the following table

1	Carbohydrates	58 %	5	Minerals	1.49 %
2	Protein	20.5 %	6	Calcium	0.98 %
3	Lipid	3.4 %	7	Phosphorus	0.53 %
4	Cellulose	3.1 %	8	Moisture	12 %
Total 100%					

Plant material :

The Leaves of Mimusops laurifolia were collected from the Egyptian museum garden, Cairo, Egypt from July to August 2018.

Extraction and Fractionation:

a. Preparation of 80% Methanol Extract :

Hydromethanol (80%) extract was prepared by cold maceration technique. Briefly, 500 g of coarse Leaves powder in a conical flask was mixed with 2.5L of 80%methanol. The flask with its contents was sealed and kept for a period of 48 h at room temperature accompanying intermittent shaking using miniorbital shaker (Bibby Scientific Limited, Stone, Staffordshire, UK) revolving at 120 rpm to enhance the efficient extraction. The entire mixture was first filtered through a funnel plunged with muslin cloth two times and then the filtrate was passed through Whatman filter paper (Number 1) (Maidstone, UK).

After filtration, the residue was remacerated two times for a total of 96 h in order to obtain a better yield. The marc was pressed and the combined filtrate was then concentrated using a rotary evaporator (Buchi Model R-200, Switzerland) set at 40 C. The concentrate was pooled together and freezedried using a lyophilizer (Operan, Korea Vacuum Limited, Korea). It rendered a solid residue of yellowish color which was designated as 80% MeOH-E and stored in an air tight container in deep freezer (−20 C) until being used for further investigation.

b. Fractionation of Crude Extract :

Solvent fractionation of crude extract was carried out using water, chloroform, and n-butanol. Briefly, eighty grams of the crude extract was dissolved in 400mL of distilled water and this solution was transferred to a separating funnel. An equal volume of chloroform was added to it and was shaken vigorously. The mixture was separated in two layers. The chloroform layer (lower) was then removed. The partition with chloroform was repeated two times. All of the chloroform layers were combined and subjected to evaporation using a rotary evaporator (Buchi Model R-200, Switzerland) set at 40 C to get the chloroform fraction, and then the filtrate was placed in an oven at 45 C for one week to remove the remaining solvent. To the separating funnel containing aqueous layer, 400mL of n-butanol was added.

The upper layer in this case was n-butanol, which was separated and the procedure was repeated two times. The separated n-butanol layers were pooled and concentrated using a rotary evaporator (Buchi model R-200, Switzerland) set at 40C to obtain the n-butanol fraction, and then the filtrate was placed in an oven at 45C for two weeks to remove the remaining solvent. The remaining aqueous layer (lower in this case) was concentrated in a lyophilizer (Operan, Korea Vacuum Limited, Korea) to remove water. After drying, the solvent fractions were stored in an air tight container in refrigerator until being used for evaluation of phytochemical constituents (**Molla et al., 2017**).

Experimental animals :

Sixty (60) male albino rats, 6-8 weeks old, with average body weight 150-200 gm used in the experimental investigation of this study, and purchased from "The Laboratory Animals Research Center", Faculty of Veterinary Medicine, Benha University. Rats were housed in separate wire mesh cages, exposed to good ventilation, humidity and to a 12-hr light/dark cycle, and provided with a constant supply of standard pellet diet (its composition is explained in the table below) and plenty of fresh, clean drinking water ad-libitum.

Experimental design :

Rats were allocated into six groups consisting of 10 rats in each, placed in individual cages and classified as following: (Group 1): serves as Normal –control group and provided with standard pellet diet only (Group 2): Receive oral dose of Mimusops Larifolia Leaves butanol extract (M.Bu E) at 75.83 mg/kg b.wt. for 8 weeks, (Group 3): Receive oral dose of (M.Bu E) at 151.66 mg/kg b.wt. for 8 weeks, (Group 4): fed on high fat diet daily for 2 months and servcd as HFD stressed group (Group 5): fed on high fat diet daily for 8 weeks; for induction of oxidative stress, besides it receive oral dose of (M.Bu E) at 75.83 mg/kg b.wt. (Group 6): fed on high fat diet daily for 8 weeks; for induction of oxidative stress, besides it receive oral dose of (M.Bu E) at 151.66 mg/kg b.wt .

N.B:

During the experimental period, the dosage was adjusted every week according to any change in body weight to maintain similar dose per kg body weight of rat over the entire period of study for each group.

Sampling :

At end of the 4th and 8th weeks from onset of experiment period, blood samples were collected from all animals groups (control and experimental groups) . Samples were collected from medial canthus of the eyes of all animal groups and were centrifuged at 3000 rpm for 30 minutes to separate serum. The non hemolyzed carefully separated serum was transferred into clean dry eppendorf tube which kept frozen at -20°C until used for biochemical analysis.

RESULTS

The obtained data revealed that, administration of mimusops laurifolia extract (at a dose of 80 and 160 mg/kg b.wt.) only to normal rat groups (G2 & G3) exhibited a significant increase in blood SOD, GSH-Px activities, and Nitric oxide concentrations on contrast, It exhibited a significant decrease in serium L-MDA concentration meanwhile,

It exhibited non significant decrease in IL-6, CRP concentrations after 4^{th} and 8^{th} weeks when compared with control normal group .

HFD Supplementation to normal rat group (G4) for 2 months exhibited a significant decrease in blood SOD, GPx activities and Nitric oxide concentration, whereas It exhibited

a significant increase in L-MDA, IL-6, CRP concentrations when compared with control normal group.

The obtained data revealed that, administration of mimusops laurifolia extract (at a dose of 80 and 160 mg/kg b.wt.) to HFD-stressed rat groups (G5 & G6) respectivily exhibited a significant increase in SOD, GPx activities and Nitric oxide

concentrations whereas It exhibited a significant decrease in L-MDA, IL-6, CRP concentrations after 4th and 8th weeks when compared with none treated HFD-stressed group (G4) .

Table 1: Effects of Mimusops Larifolia Butanolic Extract on different biochemical parameters

Group	Time	SOD (U/ml)	IL-6 (pg/ml)	Nitric oxide (µmol/L)	CRP (mg/L)	GSH-Px (mU/ml)	L-MDA (nmol/ml)
G1	After 4 weeks	3.81 ± 0.32^{c}	7.38 ± 0.29^{d}	27.34 ± 2.96^{a}	2.76 ± 0.18^{d}	67.80 ± 3.78^{b}	43.86 ± 4.03^{d}
	After 8 weeks	3.97 ± 0.36^{c}	7.45 ± 0.22^{d}	28.89 ± 3.00^{a}	2.98 ± 0.22^{d}	59.69 ± 3.34^{b}	44.28 ± 2.43^{c}
G2	After 4 weeks	4.85 ± 0.36^{b}	7.27 ± 0.20^{d}	30.96 ± 2.55^{a}	2.56 ± 0.12^{d}	84.41 ± 2.87^{a}	29.51 ± 2.04^{e}
	After 8 weeks	5.24 ± 0.37^{b}	6.89 ± 0.20^{d}	33.25 ± 2.73^{a}	2.45 ± 0.12^{d}	92.81 ± 2.61^{a}	26.21 ± 1.85^{d}
G3	After 4 weeks	6.21 ± 0.41^{a}	6.77 ± 0.20^{d}	34.06 ± 2.81^{a}	2.44 ± 0.14^{d}	92.26 ± 3.04^{a}	24.58 ± 2.11^{e}
	After 8 weeks	6.81 ± 0.75^{a}	6.45 ± 0.22^{d}	36.40 ± 2.97^{a}	2.34 ± 0.14^{d}	99.09 ± 3.52^{a}	21.22 ± 1.83^{d}
G4	After 4 weeks	1.24 ± 0.15^{d}	13.74 ± 0.42^{a}	7.86 ± 1.05^{c}	13.86 ± 0.80^{a}	25.39 ± 3.81^{e}	112.27 ± 8.66^{a}
	After 8 weeks	0.93 ± 0.10^{d}	16.14 ± 0.48^{a}	6.65 ± 0.96^{c}	18.40 ± 0.99^{a}	25.39 ± 3.81^{e}	137.17 ± 6.58^{a}
G5	After 4 weeks	3.16 ± 0.48^{c}	11.54 ± 0.60^{b}	12.87 ± 1.91^{b}	10.53 ± 0.66^{b}	37.89 ± 3.76^{d}	84.15 ± 5.35^{b}
	After 8 weeks	4.04 ± 0.58^{c}	9.88 ± 0.34^{b}	11.22 ± 1.33^{b}	9.07 ± 0.57^{b}	46.13 ± 3.09^{c}	69.13 ± 5.80^{b}
G6	After 4 weeks	3.76 ± 0.31^{c}	8.29 ± 0.32^{c}	17.04 ± 2.08^{b}	8.40 ± 0.45^{c}	49.83 ± 2.78^{c}	63.88 ± 5.29^{c}
	After 8 weeks	4.61 ± 0.38^{b}	7.94 ± 0.43^{c}	13.82 ± 2.27^{b}	6.89 ± 0.34^{c}	62.64 ± 2.93^{b}	52.12 ± 6.26^{c}

Data are expressed as (Mean ± S.E), S.E= standard error.
Mean values with different superscript letters in the same column are significantly different at : (P>0.05).
G1 = Control Group: received no drugs, provided only with a constant supply of standard pellet die for 8 weeks.
G2 = Mimusops laurifolia (Single dose) Group: provided with a constant supply of standard pellet die along with administration of Mimusops laurifolia (75.83 mg/kg b.wt.) for 8 weeks.
G3 = Mimusops laurifolia (double dose) Group: provided with a constant supply of standard pellet die along with administration of Mimusops laurifolia (151.66 mg/kg b.wt.) for 8 weeks.
G4 = High Fat Diet (HFD) Group: fed on high fat diet daily for 8 weeks; for induction of oxidative stress for 8 weeks.
G5 = HFD + Mimusops laurifolia (Single dose) Group: fed on high fat diet daily along with administration of Mimusops laurifolia (75.83 mg/kg b.wt.) for 8 weeks.
G6 = HFD + Mimusops laurifolia (double dose) Group: fed on high fat diet daily along with administration of Mimusops laurifolia (151.66 mg/kg b.wt.) for 8 weeks.

DISCUSSION

The results demonstrated that the high fat diet feeding significantly decrease blood SOD, GPx activities, whereas significantly increase serium L-MDA, IL-6, CRP and Nitric oxide concentrations compered to control normal group In all periods over the experiments .

The results of depleted SOD and GSH-Px enzymes are clarified by **(Fernández et al., 2011)** who suggested that in obese states over-consumption of oxygen, the mitochondrial and peroxisomal oxidation of fatty acids in which H_2O_2 is formed as a byproduct, generates free radicals in the mitochondrial respiratory chain that is found coupled with oxidative phosphorylation in mitochondria.

When obesity persists for a long time, The activity of SOD and glutathione peroxidase GSH-Px can be depleted due to compensation of decreased liver concentration of vitamin A having antioxidant activity In addition to decreased levels of serum antioxidants, such as vitamin E, vitamin C, β-carotene, as well as glutathione and probably indicates the dilution of fat-soluble vitamin in high liver lipid storage **(Amirkhizi et al., 2007).**

Moreover, **(Vincent and Taylor, 2006)** suggested that, Possible mechanisms contributing to the obesity associated oxidant stress include increased oxygen consumption and subsequent radical production via mitochondrial respiration, diminished antioxidant capacity, increased fat deposition, and cell injury causing increased rates of radical formation such as $O2^{-}$ and OH^{-}.In addition, hyperglycemia, hypertension, and hyperleptinemia are also possible sources of increased oxidant stress in the obese state.

On the other hand, **(Wortsman et al., 2000)** study provided that, lower antioxidant levels in individuals with increased percentage of total body fat levels may be due to the redistribution of antioxidant / antioxidant enzymes into fatty tissues, leaving fewer available in plasma and other essential sites. In support to these finding, **(Prohaska et al., 1988)** demonstrated that hepatic GSH-Px activity of obese mice was 70% of that in control lean mice and copper-zinc superoxide dismutase activity was 30% lower in obese mice.

In respect with MAD, **(Ozataa et al., 2002)** found a positive association between MDA and the body mass index (BMI) and serum triglyceride levels (which both are well known to be associated with elevated levels of insulin and resistance to insulin action exists.

Ozata et al, recorded signifcantly higher levels of malondialdehyde and 2-thiobarbituric acid reactive substances, respectively, in obese adults compared to normal-weight controls. which reflects in vivo oxidative damage to lipids. This is in agreement with **(Selvakumar et al., 2012)** who observed significant increase in levels of MDA as a marker of oxidative stress in obese subjects as compared to non obese healthy controls.

Most recently, **(Furukawa et al., 2004)** examined the relationship of lipid peroxidation (TBARS and 8-epi-PGF2a) and obesity in persons with the metabolic syndrome and found that, both BMI and waist circumference were directly correlated with plasma TBARS and urinary 8-epi-PGF2a.

Cytokines exerts many effects, ranging from defense to inflammation and tissue damage. It is produced both by macrophages and adipocytes. and by immune system cells, fibroblasts, endothelial cells, and skeletal muscle **(Fonseca et al., 2007)**.

Similarly, **(Yudkin et al., 2000)** revealed that, in healthy men and women, systemic IL-6 concentrations increase with adiposity, and it has been estimated that as much as one third of the total circulating IL-6 originates from adipose tissue.

Conversly, **(Ziccardi et al., 2002)** showed that, moderate weight loss has been found to result in decreased circulating levels of TNFα, IL-6, and CRP .

(Qatanani and Lazar, 2007) demonstrate that, diet-derived saturated fatty acids increase and activate toll-like receptors (TLRs) , expressed widely in adipocytes, both TLR2 and TLR4,on activation, mediate gene expression and synthesis of proinflammatory factors such as IL-6, and chemokines.

Moreover , **(Hye et al., 2004)** elucidated that, inflammation developed in adipose tissue of obese mice fed on HFD enhance release of proinflammatory cytokines as tumor necrosis factor alpha (TNFa) and interleukin-6 (IL-6) may be under the effect of macrophage inflammatory protein1α (MIP-1α) released from hypertrophic adipocytes and mediate inflammatory response by stimulating migration and infiltration of macrophages into obese adipose tissue and by promoting expression of chemotactic receptors thereby exacerbate adipose inflammatory signaling.

On the other hand, **(Monteiro et al., 2010)** suggested that, an increase in deregulated lipid and carbohydrate metabolism associated obesity, will increase demand on mitochondria and utilization of the electron transport chain, this will result in relative hypoxia together with increased need for nutrient oxidation which generate unusual amounts of reactive oxygen species and induce NF-κB. to increase cytokine production .

similarly, **(Pasarica et al., 2009)** reported that, Inadequate blood supply in a growing adipose tissue results in reduced oxygenation that may also contribute to inflammation.

Further, **(Michael et al., 2008)** explained that, c-reactive protein (CRP) is produced by the liver and its role in the development of inflammation has been well established. However, the strong association between CRP and risk for heart disease is a more recent discovery

Studies by **(De Ferranti and Rifai, 2002)** have shown that in vitro aggregated CRP binds to LDL and VLDL, leading to the activation of complement and the initiation of coagulation, thus explaining in part the connection between CVD and CRP .

Additionally, **(Dos Santos et al., 2008)** observed that, elevated concentrations of CRP have been associated with coronary heart disease, obesity, diabetes, smoking, and sedentary lifestyle. CRP is positively associated with F2-isoprostane levels and prothrombotic markers in obese persons, suggesting that obesity is related to a chronic state of oxidant stress and platelet activation **(Davi et al., 2002) .**

Obesity increases the risk of development of cardiovascular and metabolic diseases.

(Moncada et al., 1991) demonstrated that, endothelial nitric oxide (NO) liberated from endothelial cells and plays an essential role in dilating vascular smooth muscle , increasing regional blood flow and inhibition of platelet aggregation and adhesion, inhibition of leukocyte adhesion, and reduced smooth muscle proliferation.

(Noboru et al., 2013) reported that, obesity is associated with decreased nitric oxide

Noboru, revealed that, NO production is decreased in obese patients due to impaired endothelial NO synthase enzyme (eNOS) activity and expression, increased production of superoxide anion and endogenous eNOS inhibitors, together with increased vasoconstrictor factors, increased NADPH oxidase activity which in turn generate superoxide anions that react with NO generating highly toxic compounds such as peroxynitrite.

Results illustrated in table 1, revealed highest values of SOD, GPx activities but lowest values of L-MDA, after administration of mimusops laurifolia extract (at a dose of 80 and 160 mg/kg b.wt.) to HFD-stressed rat groups compered with group adminstered HFD only along the 4th and 8th weeks of the experment .

These results were supported by the findings of the study published by **(Chitra et al., 2016)** in which, hydroalcoholic extract of flowers of Mimusops elengi Linn.(ME) are used to scavenge the free radicals produced by Colchicine induced Alzhiemer's disease (AD) in rats. The results showed that Mimusops extract significantly decreased Lipid peroxidation (LPO) level in a dose dependent manner compared to other groups and significantly increased activities of SOD, GSH-Px and GSH as endogenous antioxidant status, this may be due to (ME) possess antioxidant activity and neuro protection attributed to alkaloids and saponins which are present in Mimusops elengi Linn. flower extract.

(Baynes et al., 1995) stated that, SOD has been postulated as one of the important enzymes in the enzymatic antioxidant defense system which catalyses the dismutation of superoxide radicals to produce H_2o_2 and molecular oxygen have diminishing the toxic effects caused by these radicals.

Also **(Yan et al., 1999)** mentioned that,GSH-Px plays a primary role in minimizing oxidative damage by working with Glutathione in the decomposition of H_2o_2 and other organic Hydroperoxides to non-toxic products, respectively, at the expense of reduced Glutathione.

Moreover, **(Gupta et al., 2014)** recorded that fruit and seed of Mimusops Elangi showed presence of Quercitol, ursolic acid, dihydro quercetin, quercetin, B-d glycosides of B sitosterol, alpha- spinasterol.

In this respect, **(Duarte et al., 2001)** discussed that, in several animal models of hypertension, long term administration of quercetin has been shown to restore the altered endothelial function may be due to the ability of quercetin to decrease the production of vascular $O2^-$, occurring mainly through two mechanisms: (1) direct scavenging of $O2^-$ and inhibition of $O2^-$ generating enzyme; (2) prevention of the expression of the genes involved in O_2^- production, like NADPH oxidase subunits.

NADPH oxidase comprises the major route for ROS production in adipocytes.

(Laplante et al., 2006) confirmed that, another important activity of quercetin and its metabolites is the concentration-dependent inhibition of the production of $O2^-$ dependent on NADPH-oxidase . According to **(Ronald et al., 2005)**, antioxidant activity of phenolic compounds is often associated with their redox properties, therefore it can be suggested that the phenolic extracts/fractions of Memusops

elengi show antioxidant activity through single electron transfer mechanism (SET). Similarly , **(Shaik et al., 2011),** evaluated the protective effect of leaf extract of Mimusops elengi on lipid peroxidation and activities of both enzymatic and non-enzymatic antioxidants in plasma and tissues against oxidative stress in streptozotocin (STZ) diabetic rats and revealed that, oral administration of leaves extract of M.elengi (100mg/kg body weight) for 30 days resulted in significant reduction in LPO levels coupled with increased activities of both enzymatic and non enzymatic antioxidants when compared to diabetic rats. This may be due to M.elengi Leaves extract is having good Antioxidant property, as evidenced by decreased tissue membrane damage.

Results represented revealed, lowest values of IL-6, CRP and but higher values of Nitric oxide levels, after administration of mimusops laurifolia extract (at a dose of 80 and 160 mg/kg b.wt.) to HFD-stressed rat groups compered with group adminstered HFD only along the ^{4}th and ^{8}th week of the experment .

These results was confirmed by **(Eskander et al., 2006)** who stated that, saponins of fruits of Mimusops laurifolia were reported to possess anti-inflammatory activity.

Previous phytochemical investigations of Mimusops elengi had revealed the presence of taraxerol in the bark, heart-wood and seeds **(Faheem et al., 2013).**

According to results of our study, **(Yao et al., 2013)** reported that, Taraxerol, a triterpenoid compound, possessed strong anti-inflammatory activities through inhibitory effects against prostaglandin biosynthesis produced by both cyclooxygenase-1 (COX-1) and (COX2) enzymes. and these inhibitions decreased the production of tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 induced by macrophages-treated lipopolysaccharide (LPS).

(Hina et al., 2016) demonstrate that M. elengi flower and leaves methanolic extracts possess significant anti-inflammatory activities due to strong occurrence of rich phenolic compounds such as, flavonoids.

Our results were interpreted by **(Mauro et al., 2010)** who attributed anti-inflammatory actions of flavonoids in vitro or in cellular models to decrease the expression of different pro-inflammatory cytokines/chemokines, including TNFa, IL-1b, IL-6, inhibition of the synthesis and activities of pro-inflammatory enzymes, such as cyclooxygenase-2, lipoxygenase and inducible NO synthase, inhibition of transcription factors (NF-kB), C-reactive protein(CRP) and activation of protein-1 (AP-1) and phase II antioxidant detoxifying enzymes. Moreover, **(Chun et al., 2008)** mentioned that, flavonoid intake has been inversely associated with plasma concentrations of CRP in a population study encompassing 8335 adults . These information are reinforced by **(Rangama et al., 2007)**, who recorded that, The stem bark of Mimusops elengi Linn., is reported to contain many phytochemicals such as β-amyrin, bassic acid, betulinic acid, lupeol, taraxerone, taraxerol, ursolic acid, α-spinasterol, β-D- glucoside of β-sitosterol, quercitol . Further, **(Butt and Sultan, 2009)** deduced that, the epidemiological evidence generally shows that a higher flavonoid intake is associated with lower cardiovascular diseases (CVD) and cancer risk. Recently, **(Melo et al., 2011)** mentioned that, alpha, beta-amyrin have exhibited anti-inflammatory and weight-loss potential in HFD-induced obese mice largely attributed to its modulatory effects on various hormonal and enzymatic secretions related to fat and carbohydrate metabolism and to the regulation of obesity associated inflammation.

Regarding to NO increased level, **(Masakazu et al., 2015)** observed that, the angiogenic effects of β-Amyrin, a pentacyclic triterpene, on vascular endothelial cells of human umbilical vein significantly increase nitric oxide (NO) production may be due to induced phosphorylation of Protein kinase B (PKB) and endothelial nitric oxide synthase (eNOS). Their findings suggest that β-amyrin could be a novel therapeutic agent for ischemic vascular diseases.

Moreover **(Flávia et al., 2017)** concluded that, cumulative concentrations of NO which has relaxing role to the endothelium of aortic rings contracted by Phenylephrine (PHE) in mice subjected to a HFD may be due to potential effects of alpha, beta-amyrin on relaxation through endothelium-dependent release of NO in obese states.

CONCLUSION

Based on the present study, it can be concluded that butanolic extract of Mimusops Larifolia leaves have potent pharmacological activities as an antioxidant, free radical scavenging and anti-inflammatory due to referred results that showed reduced values of :

L-MDA, IL-6, CRP, Nitric oxide and incresed that of SOD and GSH-Px which may be attributed to novel bioactive constituents from this extract and may be utilized in the treatment of oxidative stress evolved diseases. More studies are needed before utilizing these constituents in therapy and be widely acceptable.

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