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EFFECTS OF *AFRAMOMUM MELEGUETA* LEAF EXTRACT ON THE ANTIOXIDANT STATUS OF OBESE RATS

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ABSTRACT: *The study evaluated the possible effects of aqueous leaf extract of Aframomum melegueta on the antioxidant status of obese rats induced by using three models: monosodium glutamate (MSG), high fat diet (HFD) and MSG +HFD in rats with a view to employing the plant as a new class of anti-obesity agent. The study involved the preparation of aqueous leaf extract of Aframomum melegueta. Obesity was induced in rats as follows: sixty-five healthy albino rats were randomly divided into 13 groups of 5 rats each and obesity was induced by the subcutaneous injection of MSG (2 and 4 mg/g bwt) and HFD, treated with the extract of A. melegueta (200 and 400 mg/kgbwt) and standard drug, orlistat (50 mg /kg bwt). The activities of enzymatic (glutathione peroxidase, superoxide dismutase and catalase) non-enzymatic antioxidants (reduced glutathione) were evaluated. In the MSG model, there were significant decreases ($p < 0.05$) in the activities of GPx, SOD, (CAT) and reduced glutathione in the obese rats when compared to the control group. Administration of aqueous extract of A. melegueta at 400 mg/kg bwt significantly increase ($p < 0.05$) the GPx level. In the MSG+HFD model, there were significant decreases ($p < 0.05$) in the activities of SOD and reduced glutathione concentration in the obese rats when compared to the control group. Treatment with the extract (200 mg/kg bwt and 400 mg/kg bwt) significantly increased ($p < 0.05$) the activity of SOD. In the HFD model, there were significant decreases ($p < 0.05$) in the activities of SOD, catalase and reduced glutathione concentration in obese rats when compared to the control group. However, administration of the extract at 400 mg/kg bwt significantly increased ($p < 0.05$) the activities of glutathione peroxidase, superoxide dismutase, catalase and reduced glutathione concentration. The study concluded that extract of A. melegueta possesses antioxidant activities at 400 mg/kg bwt with the most apparent effect in HFD-induced obesity. The plant could be employed in the treatment and management of oxidative stress implicated in obesity and related disorders.*

KEYWORDS: Monosodium Glutamate (MSG), High Fat Diet (HFD), Obesity, *Aframomum Melegueta*, Antioxidant.

INTRODUCTION

Obesity is defined as excessive accumulation of body fat arising from a sustained or a periodic positive energy balance when energy intake exceeds energy expenditure (Hill *et al*., 2012). Medically, obesity is a condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems (Mohammed *et al.,* 2014). Susceptibility to oxidative damage is

greater in obese subjects because of depleted antioxidant sources, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), vitamin A, vitamin E, vitamin C, and β-carotene (Marseglia *et al*., 2015). Compared to normal weights patients, the activity of superoxide dismutase (SOD) in obese individuals are significantly lower (Marseglia *et al*., 2015). Moreover, it has been demonstrated that antioxidant supplementation could reduce reactive oxygen species (ROS), oxidative stress (OS), decrease the risk of complications related to obesity, and restore expression of adipokines (Poljsak *et al*., 2013).

Drugs used in the management of obesity have been reported to have several side effects, leading to withdrawal of these drugs from the market. Therefore, many studies were conducted to search for and develop new anti-obesity drugs through the use of natural products that could minimize the side effects (Yanovski and Yanovski, 2014). *Aframomum melegueta* is a plant that belongs to the ginger family, Zingiberaceae (Nwaehujor *et al.,* 2014). It is a perennial deciduous herb native to the tropics and grows at the swampy habitats of the West African coast. It possesses tufted leafy stem that can be up to 1.5 m high (Cheryl, 2007). The fruits are fleshy, indehiscent and produce spikes. It is an aromatic plant cultivated for its spicy fruit (Kokou *et al.,* 2013). The seeds have strong aromatic and pungent odour, peppery taste, pricking and slightly bitter (Kokou *et al*., 2013). The sharp and peppery taste of the seeds is caused by the aromatic ketones; 6-paradol, 6-gingerol and 6-shogaol present (Sugita *et al*, 2013). Essential oils, which are the dominating flavour components in the closely related cardamom, occur only in traces (SNNPR, 2005).

Based on ethno-medicinal information, *A. melegueta* has been reported to be efficacious in the management of weight gain, diabetes and other chronic diseases. Hence, this study was carried out to investigate the effect of aqueous leaf extract of *A. melegueta* on the antioxidant status of obese rats.

MATERIALS AND METHODS

Reagents and Chemicals: All the reagents used were of analytical grade and were obtained mainly from the following Chemical Manufacturing Companies: Sigma Chemical Company, St. Louis, Missouri U.S.A., Fluka Chemical Company and Pharmacia Fine Chemicals, Upsalla, Sweden. Diagnostic Kits for the assays of total cholesterol and triglycerides were products of Randox Laboratory Limited, Crumlin, UK.

Plant Material

Collection, identification, authentication and the extraction process of *A. Melegueta* with voucher no: IFE 17525 were done as previously described by Morakinyo *et al*. (2018).

Experimental Animals

Adult female (20) and male albino rats (10) weighing between 120-150 g were obtained from the Animal House, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife. The rats were housed in polyethylene cages and mated in ratio 1:2 (male: female) respectively at the Animal House, Department of Biochemistry, Obafemi Awolowo University, Ile-Ife and were kept under standard conditions, food and water were supplied *ad libitum*.

Induction of Obesity

Obesity was induced in rats' neonates (4 days old) with monosodium glutamate (MSG) (2 mg/kg bwt and 4 mg/kg bwt) according to the slightly modified method of Campos-Sep´ulveda *et al*. (2002) and high fat diet (HFD) according to modified method of Penka *et al*. (2013). The induction was carried out using 3 models, namely:

Model I: Induction with Monosodium glutamate (MSG)

Newborn rats (neonates) received subcutaneous injection of MSG (2mg/g bwt) on post-natal day 4, 6, 8, and 10; and later MSG (4 mg/g bwt) on post-natal day 12, 14, 16 and 18. After weaning (three weeks of birth), the rats were fed with standard diet until 16 weeks of age.

Model II: Induction with Monosodium glutamate and High Fat Diet

Newborn rats received subcutaneous injection of MSG (2mg/g bwt) on post-natal day 4, 6, 8, and 10; and later MSG (4 mg/g bwt) from post-natal day 12, 14, 16 and 18. After weaning (three weeks of birth), the rats were fed with high fat diet until 16 weeks of age.

Model III: Induction with High Fat Diet (HFD)

After weaning (three weeks of birth), the rats were fed with high fat diet until 16 weeks of age.

Grouping and Treatment of Experimental Animals

The obese rats were grouped and orally administered with the extract and orlistat (reference drug) daily for consecutive 45 days. The animals were divided as shown below:

Table 1: Grouping and Treatment of Experimental Animals

	Group	Treatment
Model I	I	Control received distilled water
	II	MSG only
	III	MSG + 50 mg orlistat/kg bwt
	IV	MSG + 200mg extract/kg bwt
	V	MSG + 400 mg extract/kg bwt
Model II	VI	MSG + HFD only
	VII	MSG +HFD + 50 mg orlistat/kg bwt
	VIII	MSG + HFD + 200 mg extract/kg bwt
	IX	MSG + HFD + 400 mg extract/kg bwt
Model III	X	HFD (High Fat Diet) only
	XI	HFD + 50 mg orlistat/kg bwt
	XII	HFD + 200 mg extract/kg bwt
	XIII	HFD + 400 mg extract/kg bwt

Preparation of Liver Homogenates

Liver homogenate (10% w/v) was prepared as earlier reported (Bode and Oyedapo, 2011). Liver (1 g) was cut into bits and homogenized in a total of 9 ml of freshly prepared phosphate buffer (pH 6.8, 100 mM). The homogenate was centrifuged at 3000 rpm with Bench Centrifuge for 10 min. The supernatant was carefully transferred into clean vial bottles and kept frozen at -4°C for further biochemical assays.

Biochemical Analyses

(a) Estimation of Enzymatic Antioxidants.

(i) Glutathione Peroxidase (GPx) Activity: The assay of GPx activity was carried out according to the method of Rotruck *et al*. (1973) based on catalytic oxidation of glutathione by hydrogen peroxide (H_2O_2).

The GPx activity was estimated using the expression:

$$\text{GPx activity } (\mu\text{mol/mg protein}) = \frac{\text{O. D}_{412}\ \text{X TV X df}}{6.22\ \text{X } 10^3\ \text{X EV}}$$

Where O.D = Absorbance at 412; df = dilution factor; extinction coefficient = 6.22 X 10^3,

EV = enzyme volume and TV = Total Volume

(ii) Superoxide Dismutase (SOD) Activity: The assay of liver superoxide dismutase activity was carried out according to the method of McCord and Fridovich (1969) based on the inhibition of auto-oxidation of pyrogallol at pH 8.2.

$$\text{Percentage Inhibition} = 100 - \left(100\ X\ \frac{\text{increase in absorbance of substrate}}{\text{increase in absorbance of blank}}\right)$$

1 unit of SOD activity was given as the amount of SOD necessary to cause 50% inhibition of the oxidation of pyrogallol. The activity of SOD is expressed as Unit/mg protein.

(iii) Assay of Catalase Activity: Assay of liver catalase activity was carried out according to the method of Aebi (1982) based on the catalytic decomposition of hydrogen peroxide to form water by catalase.

The catalase activity was calculated using the expression:

$$\text{Catalase activity (Units/ml)} = \frac{\Delta A/\text{min x d x TV}}{\text{SV x } 0.0436}$$

$\Delta A/min$ = slope of the gragh of absorbance against min

d = dilution factor

SV = Sample volume (ml)

0.0436 = Extinction coefficient for hydrogen peroxide

TV = Total reaction volume

Catalase activity (U/mg protein) = $\frac{\text{Unit/ml}}{\text{mg protein/ml}}$

One unit of activity of catalase is equal to 1 mmol of H_2O_2 degraded per minute and expressed as units per milligram of protein.

(b) Estimation of Non-enzymatic Antioxidant

(i) Glutathione (GSH) Level: The reduced glutathione level in the heart homogenate was estimated according to the method of Moron *et al*. (1979) based on the principle that GSH exerts its antioxidant action through its sulphydryl groups. The level of liver GSH was interpolated from the standard calibration curve. The values were expressed as μg GSH/g sample.

Statistical Analysis

Data are expressed as mean ± SEM. Differences between the mean values of the control and treated groups were determined by One-way Analysis of Variance with a Dunnett post hoc test using the Graph Pad Prism 5. Significant difference was considered if $p < 0.05$.

RESULTS

Effects of *A. melegueta* Extract and Orlistat on Liver Ezymatic and Non-Enzymatic Antioxidants

The summary of reduced glutathione concentration and activities of glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) in obese rats is presented in Table 2.

There were significant decreases ($p < 0.05$) in the activities of GPx, SOD, (CAT) and reduced glutathione in MSG-induced group when compared to the control group. Administration of aqueous extract of *A. melegueta* at 400 mg/kg bwt significantly increase ($p < 0.05$) the GPx level while no significant difference ($p < 0.05$) was observed in the activities of SOD, CAT and reduced glutathione concentration when treated with the extract at 200 mg/kg bwt and orlistat.

In the MSG+HFD model, there were significant decreases ($p < 0.05$) in the activities of SOD and reduced glutathione concentration in MSG+HFD-induced obesity animals when compared to the control group. Treatment with the extract (200 mg/kg bwt and 400 mg/kg bwt) significantly increased ($p < 0.05$) the activity of SOD while no significant difference ($p < 0.05$) was observed in the activities of GPx, CAT and reduced glutathione concentration when treated with the extract (200 mg/kg bwt and 400 mg/kg bwt) and orlistat.

In the HFD model, there were significant decreases ($p < 0.05$) in the activities of SOD, catalase and reduced glutathione concentration in HFD-induced obesity animals when compared to the control group. However, administration of the extract at 400 mg/kg bwt significantly increased ($p < 0.05$) the activities of glutathione peroxidase, superoxide dismutase, catalase and reduced glutathione concentration. Administration of the extract (200 mg/kg bwt) and orlistat significantly increases ($p < 0.05$) the levels of reduced glutathione and catalase.

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Table 2: Effects of *A. melegueta* Extract and Orlistat on Enzymatic and Non-enzymatic Antioxidants of Obese Rats

	Reduced Glutathione (mg/g)	Glutathione Peroxidase (U/mg protein)	Superoxide Dismutase (Unit/min/mg Protein)	Catalase (U/mg protein)
Control	11.23 ± 0.14	24.31 ± 2.37	9.08 ± 0.33	6.58 ± 0.40
MSG only	10.42 ± 0.14[a]	11.17 ± 0.66[a]	4.74 ± 0.31[a]	1.64 ± 0.59[a]
MSG + orlistat 50 (mg/kg bwt)	10.14 ± 0.13	23.19 ± 3.50	5.22 ± 0.71	2.71 ± 0.21
MSG + AM 200 (mg/kg bwt)	10.69 ± 0.15	24.03 ± 4.60	5.57 ± 1.04	2.75 ± 0.77
MSG + AM 400 (mg/kg bwt)	10.77 ± 0.24	34.30 ± 1.07[b]	6.47 ± 1.34	3.59 ± 1.05
MSG + HFD only	10.44 ± 0.22[a]	12.98 ± 0.70	3.65 ± 0.11[a]	2.29 ± 0.52
MSG + HFD+ orlistat 50 (mg/kg bwt)	11.03 ± 0.18	12.79 ± 0.09	4.50 ± 0.39	5.35 ± 1.76
MSG + HFD + AM 200 (mg/kg bwt)	10.78 ± 0.17	13.05 ± 0.37	5.27 ± 0.18[b]	3.36 ± 0.76
MSG + HFD+ AM 400 (mg/kg bwt)	10.39 ± 0.22	15.49 ± 1.10	5.79 ± 0.23[b]	5.96 ± 1.01
HFD only	9.59 ± 0.32[a]	15.92 ± 0.93	2.60 ± 0.11[a]	1.46 ± 0.27[a]
HFD+ orlistat 50 (mg/kg bwt)	10.66 ± 0.11[b]	16.29 ± 3.74	5.21 ± 1.84	5.17 ± 0.07[b]
HFD+ AM 200 (mg/kg bwt)	10.77 ± 0.19[b]	12.53 ± 1.03	3.46 ± 0.14	3.31 ± 0.38[b]
HFD+ AM 400 (mg/kg wt)	10.58 ± 0.13[b]	27.63 ± 3.32[b]	8.51 ± 0.15[b]	4.13 ± 0.45[b]

Each value represented Mean ± SEM, n = 5 readings. Value of p <0.05 was considered significant. The values across column with superscript (a) implied significant difference from control while (b) implied significant difference from MSG, MSG+HFD and HFD groups.

MSG- Monosodium glutamate, HFD-High fat diet, AM- A. melegueta

DISCUSSION

In the present study, the effects of aqueous extract of *A. melegueta* were investigated in obese rats by using using three models: administration of monosodium glutamate (MSG), high fat diet (HFD) and the combination of MSG and HFD. It has been established that injections of monosodium glutamate to new born rats caused lesion in the ventromedial region of the hypothalamus, leading to obesity due to the loss of control (by the organism) on the absorption and expenditure of energy (Dolnikoff *et al*., 2001).

Some bioactive compounds like saponins, flavonoids, and some triterpenoids in various plants have been noted for their anti-obesity effect (Yun *et al.,* 2010). Flavonoids are found ubiquitously in plants and they are the most common group of polyphenolic compounds that

exhibit antioxidant activities. Saponins have been shown to lower cholesterol concentration by competing against it for absorption in the body. It is also known to boost the immune system (Ostlund *et al.,* 2003). It was reported in our previous studies that *A. melegueta* contained an appreciable quantities of flavonoids, alkaloids, tannins, saponnins and sterols (Morakinyo *et al*., 2018)

It has been shown that animal system had an effective mechanism to prevent the free radical induced tissue cell damage, when the balance between ROS production and antioxidant defense is lost oxidative stress results; this is accomplished by a set of endogenous antioxidant enzymes and protein such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and reduced glutathione (GSH). This, through a serious of events deregulates the cellular functions leading to various pathological conditions (Noeman *et al*., 2011; Ebele *et al*., 2016).

Catalase and glutathione peroxidase constituted a mutually supportive team of defense against reactive oxygen species. The result clearly revealed a significant decrease ($p < 0.05$) in the activities of SOD, GPx and CAT and reduced glutathione in the liver homogenates in MSG only treated rats as compared to the control group. There were no significant ($p < 0.05$) changes in the activities of catalase and glutathione peroxidase in hepatic tissue of MSG+HFD compared to the control group. The HFD-induced obese rats showed a non-significant ($p < 0.05$) change in the activity of glutathione peroxidase when compared to the control group. The results were in agreement with previous authors (Lannaud-Bournoville *et al*., 1999; Vincent *et al.,* 2010; Olusi *et al*., 2002, and Moya *et al*., 2008). Furukawa *et al.* (2004) observed reduced SOD, GPx, and CAT activities in adipose tissue, but not in the liver obese mice. *Noeman et al.* (2011) reported decrease in the activity of GPx, but not CAT in the hepatic tissue of obese rats. Such differences in the activities of antioxidant enzymes in obese state can be caused by different obesity models and differences between early stages of obesity and chronic obesity (Vincent and Taylor, 2006). The administration of the extract in the HFD-model significantly increased ($p < 0.05$) the level of CAT, GPx, SOD and reduced gluthathione in the treated rats.

Superoxide dismutase, catalase and glutathione peroxidase are antioxidant enzymes which do not only play fundamental but indispensable role in the antioxidant protective capacity of biological systems against free radical attack (Asadi, 2013). The superoxide radical ($O_2^{\bullet -}$) or singlet oxygen radical ($^1O_2$) generated in tissues through metabolism or reactions in cells is catalytically converted to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) by superoxide dismutase (SOD) (Johansen *et al*., 2005; Ighodaroa and Akinloye, 2018). The accumulation of H_2O_2 is toxic to body tissues or cells. Also, in the presence of Fe^{2+} it is converted to deleterious hydroxyl radical (^+OH) through Fenton reaction. In order to prevent this phenomenon, catalase which is abundant in the peroxisomes breaks down H_2O_2 into water and molecular oxygen, consequently curtailing free radical-induced damage. However, catalase is absent in the mitochondria, hence the reduction of H_2O_2 to water and lipid peroxides to their corresponding alcohols is carried out by glutathione peroxidase (GPx) (Ighodaroa and Akinloye, 2018). GSH reduces H_2O_2 and lipid peroxides via reactions catalyzed by GSH peroxidase(Eroglu *et al*., 2015).

The ability of the aqueous extract of *A. melegueta* to bring a significant increase ($p < 0.05$) in the levels of the enzymatic and non-enzymatic antioxidant parameters might be due to the presence of phytoconstituents.

CONCLUSION

In conclusion, the ability of the extract to manage oxidative stress implicated in obesity was demonstrated. It is evident from our previous studies that aqueous leaf extract of *A.melegueta* contained phytochemicals that could lead to observed antioxidant activities. The plant, *A. melegueta* could therefore be used in the management and treatment of obesity related diseases.

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