Original Article

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Effect of Ketogenic Diet on Monosodium Glutamate-Induced Uterine Fibroids in Female Wistar Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: Ketogenic diet (KGD) is a low-carbohydrate, high-fat and average protein dietary formulation, which has been reported with the ability to ameliorate several metabolic diseases, especially those under the direct influence of hormonal disruptions. Monosodium glutamate (MSG) had been found to induce uterine fibroids in laboratory animals through alterations to hormones, lipids and oxidative state. The present study was conducted to evaluate the effect of KGD on MSG-induced uterine fibroid.

METHODS: In this experimental study twenty-four female Wistar rats were divided into four groups of six. Control group received distilled water while the remaining groups were given 300 mg/kg body weight of MSG once a day for 28 days. Thereafter, the three groups of MSG, MSG + keto group 1 and MSG + keto group 2 received standard rat chow, cabbage-based ketogenic diet and coconut-based ketogenic diet, respectively for 42 days. Estrogen, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), malondialdehyde (MDA), Superoxide Dismutase (SOD), catalase (CAT), and Total Cholesterol (TC) were determined in the blood of animals using standard methods and induction of fibroids was confirmed in the uterus by histomorphological measurements.

FINDINGS: Significant elevations ($p<0.05$) were observed in the levels of estrogen (1.80±0.09 &1.27±0.12), LH (1.04±0.04 & 0.39±0.01), FSH (1.51±0.04 & 0.65±0.03), TC and MDA in the MSG group compared to control. There were significant decreases ($p<0.05$) in the activities of CAT and SOD enzymes in the MSG group compared to control. Histological analysis confirmed significant reduction ($p<0.05$) in leiomyomas of the dietary treatment groups compared to that of MSG.

CONCLUSION: The study suggests that cabbage- and coconut-based KGD may control the occurrence and progression of fibroids through reduction of oxidative damage and amelioration of hormonal imbalance induced by MSG.

KEY WORDS: *Ketogenic Diet, Monosodium Glutamate, Uterine Fibroid, Sex Hormones, Oxidative Damage*.

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Introduction

Monosodium glutamate (MSG) is the salt of the non-essential amino acid glutamate, which increases appetite by stimulating the appetite center in the hypothalamus. There are certain reports indicating that MSG is toxic to both experimental animals and human beings through induction of lipid dysfunction, testicular dysfunction, obesity and uterine fibroid among others (1-5). MSG induces uterine fibroid in rats by increasing the level of estrogen, cholesterol and total protein (6). MSG is also implicated in the induction and progression of oxidative stress in experimental animals (2).

Oxidative stress describes a condition of imbalance between oxidative radicals and antioxidant defense system (superoxide dismutase, catalase, glutathione, etc.) such that the former is grossly inadequate to combat the radicals, thus leading to the onset of the condition. Antioxidant enzymes play an important role in limiting cellular stress. Superoxide dismutase scavenges O_2 radical by converting superoxide to H_2O_2 and molecular oxygen while catalase brings about the reduction of H_2O_2 and protects tissues from highly reactive hydroxyl radicals (7).

Oxidative stress has been linked to almost all metabolic diseases and has the ability of initiating tissue and eventually organ dysfunction (7). Oxidative stress also enhances progression of tumor growth either malignant or benign such as leiomyomas (8, 9). Uterine fibroids are benign tumors, or leiomyomas of the smooth muscle compartment of the uterus (10-12). Uterine fibroid occurs in most women of reproductive age (13). The symptoms include heavy and irregular bleeding, pelvic pain and pressure, bowel and bladder dysfunction, early pregnancy loss and preterm labor (14). Uterine fibroids are likely to occur in 80% of women by the age of 50 (15). Only 20% to 50% of women are symptomatic although most cases are detected incidentally on imaging in asymptomatic women (15). The pathogenesis is multifactorial, and includes sex hormones such as progestogens and estrogens that proliferate tumor growth, as well as oxidative stress, genetic factors and cytokines (9).

Ketogenic diet (KGD) is a high-fat, low-carbohydrate diet, with enough protein content, which makes the body utilize fat, rather than carbohydrate, as a preferred energy source (16). When a diet rich in carbohydrate is ingested, the substrate generates glucose, which produces ATP for all the organs of the body, including the brain. Ketogenesis is activated in the liver whenever there is a reduction in carbohydrate intake; this catabolizes fat and makes fatty acids and ketone bodies (17). These ketone bodies are able to cross the blood–brain barrier and provide energy to the brain. Other organ systems also use ketones as an efficient energy source (17). KGD is used as a therapy for weight loss and metabolic function improvement, such as management option for epilepsy, convulsion, reproductive dysfunction, diabetes, heart diseases and tumor growth (1, 18-22).

The treatment of uterine fibroid is classically done through surgery; however, various medical options are available, which provide symptom control while minimizing risks and complications. A large number of clinical trials have evaluated the commonly used medical treatments and potentially effective new ones (23). The two major leading and most promising drugs for uterine fibroids are orally active gonadotropin-releasing hormone receptor (GnRH) blockers and progesterone receptor (PR) modulators (24). Nutrition as a therapy for treatment of toxicity is usually without consequences or adverse side effects and usually cheaper, readily available, and non-invasive. This study explores the option of nutritional control using KGD as an ameliorative tool for monosodium glutamate-induced uterine fibroid in female Wistar rats.

Methods

This experimental study was approved by the ethics committee of Department of Biochemistry, Landmark University Animal Care Committee with the code of LUAC-0038B.

Experimental animals: Twenty-four (24) healthy female Wistar rats weighing 152±12 g were obtained from Biochemistry Animal House, University of Ilorin, Ilorin, Nigeria. The rats were acclimatized for 14 days and during the experiment, they were housed in wooden cages in the animal house of the department of Biochemistry, Landmark University Kwara State, under standard conditions. The animals had access to clean drinking water and rats pellet ad libitum.

Monosodium Glutamate (MSG) reagent: MSG was purchased from Sigma Aldrich Chemical Co., St Louis, USA and a stock solution was prepared by dissolving 30 g of MSG in 300 mL of distilled water. With reference to the animals' weights, 300 mg/kg MSG was administered to all the treatment groups once a day for twenty eight days as previously reported (with slight modification) for induction of uterine fibroids in female Wistar rats (25).

Chemical and Reagents: Reagent kits used for assay of total cholesterol and triglyceride were products of

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Randox Laboratory Limited, UK. All other reagents used were of analytical grade.

KGD preparation/formulation: Novel preparation and formulations of low-carbohydrate fibers were made from cabbage and coconut in our laboratory, Department of Biochemistry, Landmark University. Components and ingredients of the diet includes cabbage/coconut (500 g), protein (100 g), fat (250 g), vitamin/minerals (100 g) and food binders (50 g) for every kilogram formulation. The ingredients were thoroughly mixed and water was added to make dough. The dough was rolled, cut into different sizes, and dried in oven at 70 ^{o}C for 2 h as described by Kayode et al. (1).

Animal Treatment and biochemical assays: The rats were randomly distributed into four groups of six. Control group received distilled water. The monosodium glutamate group (MSG group) received 300 mg/kg of MSG for 28 days. The MSG+keto group 1 was treated with 300 mg/kg body weight of MSG for 28 days followed by cabbage-based ketogenic diet for 42 days while MSG+keto group 2 received 300 mg/kg body weight of MSG for 28 days followed by coconut-based ketogenic diet for 42 days. Treatment was done via oral administration as a single daily dosage. A day after the final exposure, the animals were sacrificed. Blood sample was collected by cardiac puncture into plain sample bottles, and the uterus, kidney, and liver tissues were excised. The serum was prepared by centrifugation at 2500 x g for 15 min and used in determination of hormonal and biochemical assays.

Hormonal assays: Oestrogen, Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) levels were determined in the serum based on the principle described by Tietz (26).

Lipid Assay: Serum triglyceride was determined according to the principle described by Mochin and Leyva (27). Serum total cholesterol was determined according to the method described by Fredrickson et al. (28).

Lipid peroxidation and antioxidant enzymes: The superoxide dismutase (SOD) activity was determined according to the method described by Misra and Fridovich (29). Catalase (CAT) activity was determined according to the method of Singha (30). Malondialdehyde (biomarker for lipid peroxidation) activity was determined according to the method of Satoh (31). Biuret method was used to evaluate the protein concentration of the liver, uterus, kidney and serum as described by Gornall et al. (32).

Histology: Histological analysis was carried out to confirm the onset of uterine fibroid in the rats. Uterus tissue of each rat was stained with hematoxylin and eosin (Sigma) and examined under a microscope (Nikon ECLIPSE Ni-U, Tokyo, Japan) at 400×magnification. Images were captured from 10 randomly selected fields per rat, and endothelial thickness was measured using ImageJ software (ImageJ v46a; NIH, U.S.A.).

Statistical analysis: Data were expressed as mean±standard error of mean (SEM) and analyzed with one-way ANOVA and student t-test using GraphPad Prism 6 (GraphPad Software Inc., San Diego, California, USA). Tukey's post-hoc test was used to compare mean values and $p<0.05$ was considered statistically significant.

Results

All the treated animals experienced changes in weight during the course of the experiment when compared to the control. The MSG + Keto groups 1 and 2 showed significantly reduced ($p<0.05$) weight compared to the animals treated with MSG, which had significant weight gain ($p<0.05$) in comparison with the control (Table 1). The concentration of estrogen was elevated in the animals treated with MSG when compared with the control animals. The estrogen levels were significantly ($p<0.05$) reduced in those under ketogenic diet, with MSG + Keto group 1 showing greater estrogen level reduction (Table 2). Similar patterns were observed in the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the experimental groups (Table 2).

The animals treated with MSG showed significantly increased ($p<0.05$) levels of cholesterol when compared to the control; this was significantly ($p<0.05$) decreased in the MSG + Keto groups 1 and 2 when compared to the MSG-treated animals (Figure 1). The animals administered with MSG showed significantly ($p<0.05$) elevated levels of malondialdehyde in the tissues when compared to the control group. These were consequently lowered in the MSG+Keto groups 1 and 2 in the organs when compared to the MSG group (Figure 2).

The animals administered with MSG showed significantly depleted ($p<0.05$) antioxidants enzymes activities (SOD and CAT) in the tissues when compared to the control. These were significantly ($p<0.05$) reversed in varying degrees in the MSG + Keto groups 1 and 2 (Figures 3 and 4). The photomicrographs of

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control animals shows that the connective tissues and endometrial cells are normal (Figure 5 A). This normal architecture (seen in the control group) has been disrupted in the animals treated with MSG. Severe hyperplasia of the precursor cells was observed in this group (Figure 5 B). However, animals in MSG + Keto group 1 showed normal outline of the precursor cells and absence of hyperplasia in the endometrium (Figure 5 C), while animals in MSG + Keto group 2 showed significant reduction of hyperplasia of the precursor cells of the endometrium when compared with the MSG-treated animals (Figure 5 D).

Table 1. Effect of KGD on the weights of rats with MSG induced fibroids

Groups	Initial weight (g)	Final weight (g)	Difference in weight (g)	Percentage of weight gain (%)	Percentage of weight loss (%)
Control	175.13±3.5	188.99±3.9	13.86	7.33	-
MSG	161.20±5.5	180.74±6.5	19.5	10.79	-
MSG+keto group 1	147.76±4.8	119.72±7.5	28.04	-	23.42
MSG+Keto group 2	159.79±5.2	144.70±1.5	15.09	-	10.42

Table 2. Effect of KGD on Estrogen and gonadotropin concentration in Wistar rats with MSG induced uterine fibroid

Groups	Estrogen (IU/ml)	FSH (IU/ml)	LH (IU/ml)
Control	1.27 ± 0.12^{b}	0.65 ± 0.03^{a}	0.39 ± 0.01^{a}
MSG	1.80 ± 0.09^{c}	1.51 ± 0.04^{c}	1.04 ± 0.04^{b}
MSG+keto group 1	0.60 ± 0.03^{a}	0.62 ± 0.02^{ab}	0.51 ± 0.01^{a}
MSG+Keto group 2	1.00 ± 0.05^{b}	0.75 ± 0.02^{b}	0.57 ± 0.01^{a}

Values are expressed as Mean±SEM. Values bearing different alphabets are significantly different (p≤0.05).

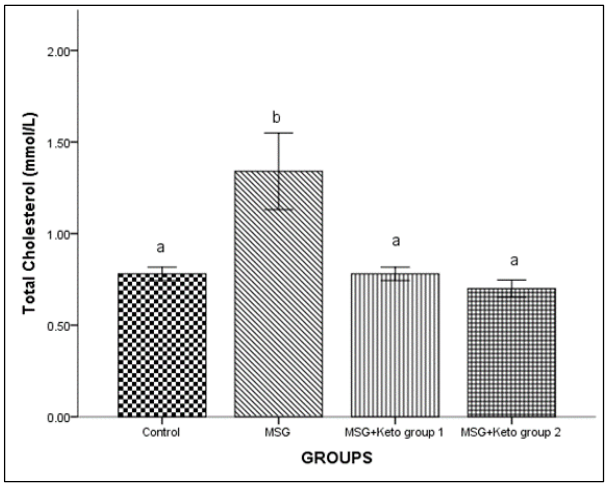

Figure 1. Effect of KGD on serum total cholesterol in Wistar rats with MSG-induced uterine fibroid. Values are expressed as Means±SEM. Values with different alphabets are significantly different (p≤0.05).

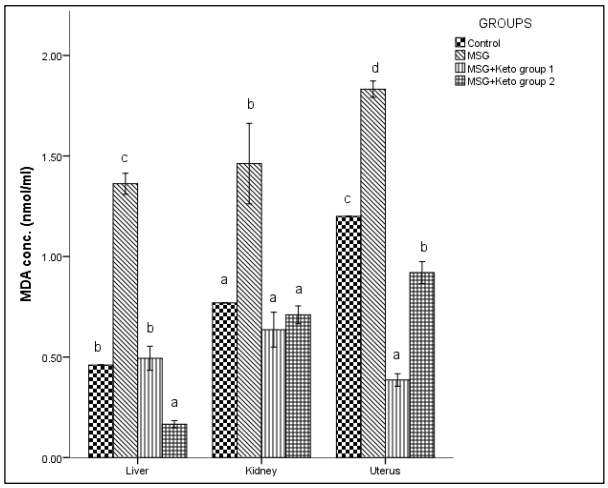

Figure 2. Effect of KGD on malondialdehyde in Wistar rats with MSG-induced uterine fibroid. Values are expressed as Means±SEM. Values bearing different alphabets are significantly different (p≤0.05).

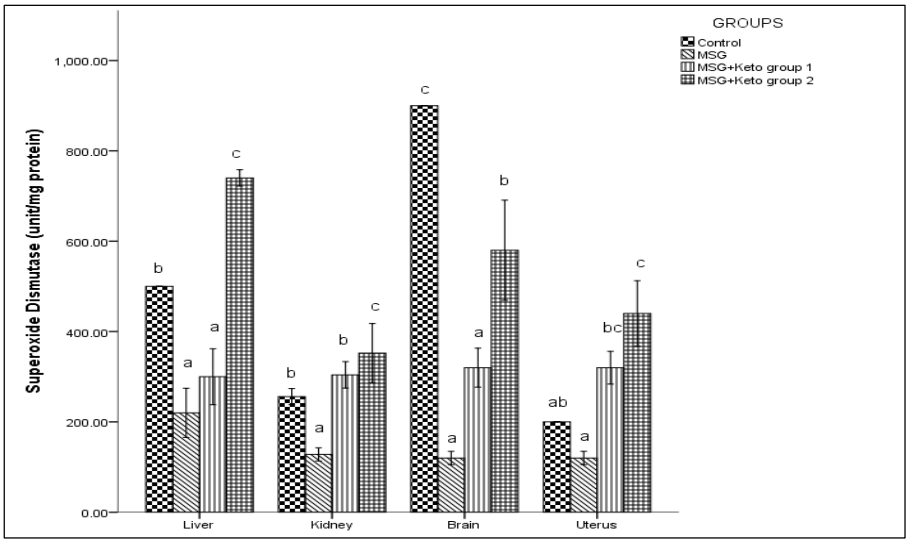

Figure 3. Effect of KGD on SOD activity of selected tissues in Wistar rats with MSG-induced uterine fibroid. Values are expressed as Means ± SEM. Values bearing different alphabets are significantly different (p≤0.05).

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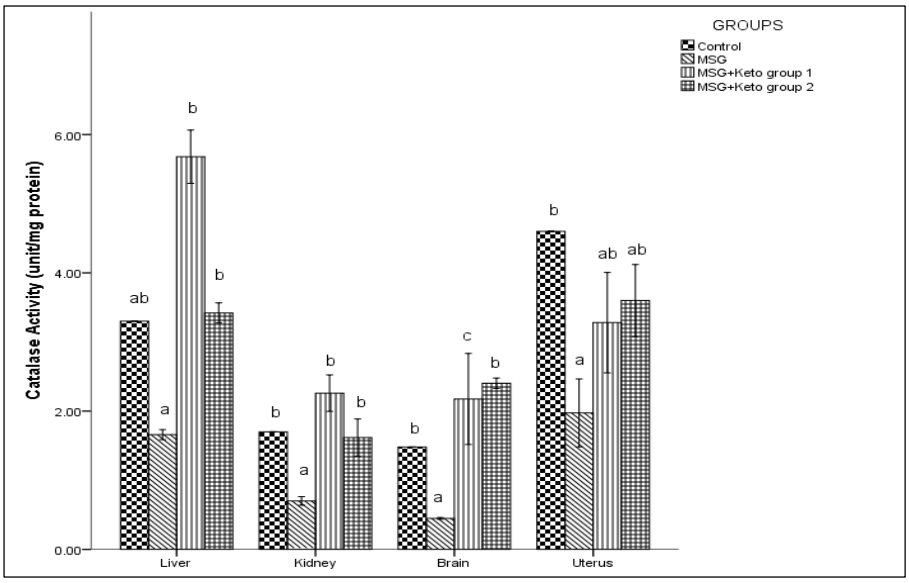

Figure 4. Effect of KGD on catalase activity of selected tissues in Wistar rats with MSG induced uterine fibroid.

Values are expressed as Means ± SEM. Values bearing different alphabets are significantly different ($p \leq 0.05$).

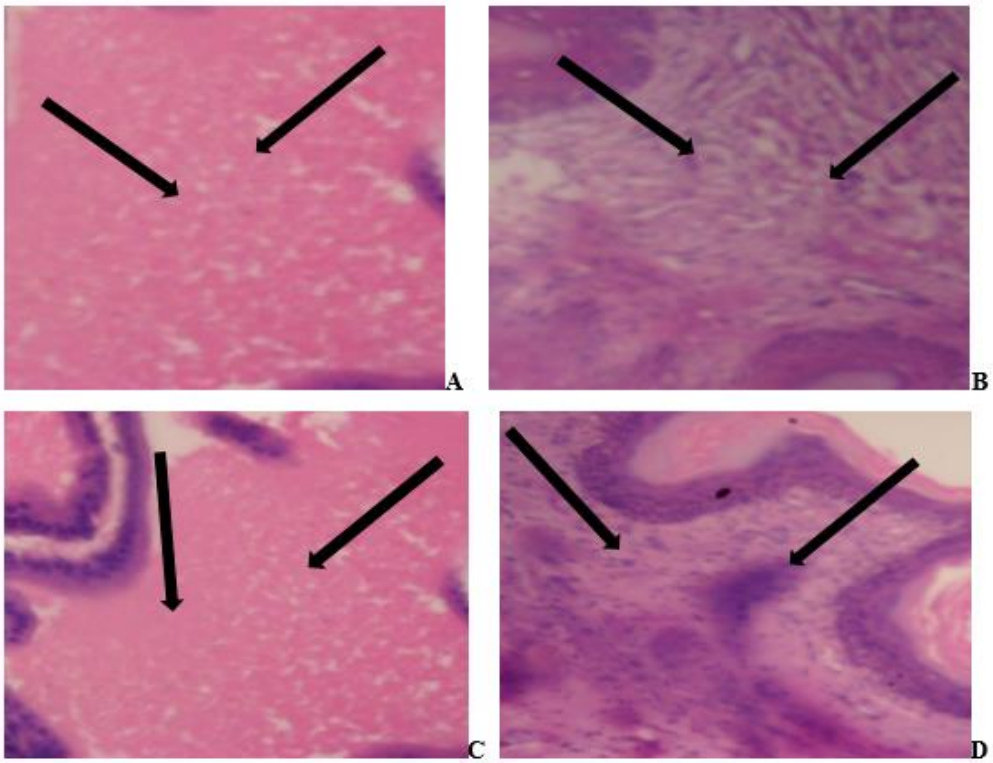

Figure 5. Representative photomicrograph of hematoxylin and eosin stained uterus of the control and treated animals (A-D).

A: Photomicrograph of hematoxylin and eosin stained uterus of control animals showing normal connective tissues and endometrial cells outline at X400 magnification

B: Photomicrograph of hematoxylin and eosin stained uterus of MSG-treated animals showing severe hyperplasia of the precursor cells (spindle shaped) of the endometrium at X400 magnification

C: Photomicrograph of hematoxylin and eosin stained uterus of MSG+KG1-treated animals showing normal outline of the precursor cells (spindle shaped) and absence of hyperplasia in the endometrium at X400 magnification

D: Photomicrograph of hematoxylin and eosin stained uterus of MSG+KG2-treated animals showing significant reduction of hyperplasia of the precursor cells (spindle shaped) of the endometrium at X400 magnification

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Discussion

The administration of the two ketogenic diets in this study ameliorated the biochemical alterations associated with MSG-induced uterine fibroids in the Wistar rats. MSG treatment led to a significantly ($p<0.05$) increased weight gain in the animals compared with the control. This finding is in line with previous reports and suggests the ability of chronic consumption of MSG to initiate obesity-related condition in animals and humans (3, 33, 34). Administration of KGD however significantly ($p<0.05$) reduced the weight of the animals (especially those of the cabbage-based formulation), hence supporting previous reports on the use of the diet for achieving effective weight loss in animals (19, 35, 36).

The increase in the level of estrogen in the MSG-treated animals may indicate an increase in the activation of the enzyme aromatase, which catalyzes the conversion of testosterone to estradiol, therefore resulting in elevated estradiol synthesis (37-39). KGD administration was able to ($p<0.05$) reduce the levels of circulating estrogen significantly in the serum using the coconut-based diet, which achieved a higher reduction when compared to the control. Growth of uterine fibroids had been associated with increased levels of estrogen (10, 39). Therefore, the inherent ability of the ketogenic diet to limit the levels of serum estrogen might be one of the mechanisms by which it shrinks the myeloma in the uterus.

The level of FSH and LH, which are precursors directing the production of estrogen in a concentration-dependent manner, was significantly increased ($p<0.05$) in the MSG-treated group probably due to the overproduction of gonadotropin releasing hormone (GnRH), which stimulates the production of LH and FSH from the pituitary gland (40). MSG may therefore direct the onset of hormonal imbalance in females, which often occur prior to the onset of uterine fibroids (41). The KGD ameliorated this increase by significantly reducing ($p<0.05$) the levels of the gonadotropins, which will ultimately contribute to the reduction in estrogen levels.

Obochi et al. (6) reported that MSG administration leads to increase in cholesterol, and estrogen levels, which lead to the induction of fibroid in rats. This is in line with our findings of significant increase ($p<0.05$) in the total cholesterol level for the MSG-treated group when compared to the control group, hence indicating that MSG may cause disorder in lipid metabolism in rats on chronic exposure (25, 42). The elevated serum total cholesterol was however significantly lowered ($p<0.05$) by the two KGD used in this study. The diet may therefore be useful in managing disease conditions associated with lipid metabolism derangement besides uterine fibroids.

Lipid peroxidation is a marker of oxidative stress (8) and malondialdehyde, which is a by-product of lipid peroxidation, was observed to be elevated in the MSG-treated animals, thereby suggesting that MSG treatment alone may foster the generation of reactive oxygen species (8). Oxidative stress has been implicated previously in uterine fibroids and suggested as one of the mechanisms that is initiated and proliferated (9). KGD administration however caused a significant reduction ($p<0.05$) in MDA levels suggesting its antioxidant and ameliorative potential against MSG-induced fibroids.

Treatment of the animals with MSG brought about a significant decrease ($p<0.05$) in the activities of the measured antioxidant enzymes, hence predisposing the cells to higher probability of oxidative radicalization. The KGD treatment conversely resulted in significant increase ($p<0.05$) in the activity of these enzymes when compared to the MSG-administered group. This observed increase may result in adequate reduction of oxidative stress and effective protection of tissues from highly reactive hydroxyl radicals (43). In addition, MSG-induced uterine hyperplasia was reversed in the groups administered with KGD formulations. The outcome of this work suggest that these ketogenic diet formulations (cabbage- and coconut-based) may possess some bioactive agents that can ameliorate endometrial hyperplasia and also protect against MSG-induced elevated levels of hormones, lipids and oxidative stress that are connected with the initiation and progression of uterine fibroid in rats. A cabbage- and coconut-based KGD may ameliorate the oxidative aberration, hypercholesterolemia and over secretion of female sex hormones induced by MSG intake. The diet may therefore be effective in the management of uterine fibroid caused by repeated oral exposure to monosodium glutamate.

Conflicts of Interest: The authors declare no competing financial or non-financial interests.

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