Ginger Rhizomes as Anti-Obesity Agent in MSG – Exposed Female Rats: Anti-Hypothyroidic Effect versus Satiety Stimulation as Possible Mechanisms

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Abstract

In Egypt, overexposure to monosodium glutamate (MSG) was reported as a fundamental health challenge. Thus, dietary interventions were needed to prevent the disorders associated with this food additive, especially obesity which is still of great concern. This study was conducted to investigate both the satiety stimulating and the anti-hypothyroidic properties of ginger (*Zingiber officinale*) as mechanisms for its anti-obesity effect in female rats concurrently exposed to MSG. Twenty adult female albino rats were divided into four equal groups, including the control group, while groups 2 to 4 were administered 6 mg MSG/kg body weight daily, and kept untreated (group 2), or concurrently fed diet supplemented with 0.5 and 1 % of ginger powder (groups 3 and 4, respectively) for 6 weeks. At the end, body weight gain, feed intake and feed efficiency ratio were calculated. Leptin as well as thyroid -related hormones were determined in sera, while oxidative stress markers were determined in thyroid tissue homogenate. Moreover, specimens from thyroid tissue of rats were histopathologically examined. MSG consumption induced overweight along with increased appetite besides overt hypothyroidism, which was evidenced by increased thyroid stimulating hormone level $(0.08\pm0.01$ versus 0.00 ± 0.00 uIU/ml in healthy control). while thyroxin level was decreased (2.76±0.36 versus 3.43±0.43 ng/dl in healthy control). Disturbance of antioxidant defense system in thyroid tissue was also noticed, which was further confirmed by histological staining. Inclusion of ginger powder in rat diet prevented weight gain, which was accompanied with antihypothyroidic effects, while appetite was not affected statistically. Thus, it could be concluded that through maintaining thyroid

functions, but not reducing appetite, ginger powder prevented obesity associated with MSG consumption in female rats.

Keywords: Zingiber officinale; Body weight; Thyroid disorders; Appetite; Flavor enhancers.

Introduction

Worldwide, overweight and obesity were reported as fundamental health challenges. In 2016, more than 1.9 billion adults of 18 years or more were found to be overweight, while 650 million were obese (WHO, 2018). Decades of evidence show the positive relationship between obesity and the risk of serious health conditions including hyperglycemia, dyslipidaemia, hypertension, coronary heart disease, stroke, obstructive sleep appoea, difficult breathing and cancers (Kinlen et al., 2018). Among many health associated hyperphagia complications with obesity. and hypothyroidism were reported in females (Eckel and Moore, 2004; Wang et al., 2018). Both subclinical and overt hypothyroidism can induce changes in body weight, body composition, total and resting energy expenditure, independently of physical activity (Knudsen et al., 2005).

As a flavor enhancer, monosodium glutamate (MSG) consumption has increased all over the world in recent years (Niaz et al., 2018). In the Egyptian market, some of the food products with added MSG, especially those directed to kids like flavored potato chips, noodles, etc, were found to exceed the European limit of 10 g/kg (1%) of product. Other products may have MSG within the allowable limits, but one can ingest many of these products per day without paying attention to the total amount of MSG ingested (Abdel Moneim et al., 2018). Although approved by Food and Drug Administration (FDA), it was revealed that high MSG consumption was associated with many health problems. The most dangerous and prevalent is obesity (Kazmi et al., 2017). Various mechanisms and metabolic abnormalities associated with MSG induced overweight was outlined (Bautista et al., 2019). As a flavor enhancer, MSG was found to increase food intake in humans (Rogers and Blundell, 1990). Recently, MSG exposure, even at

low doses, was demonstrated to induce histomorphometric abnormalities in thyroid gland (Khalaf and Arafat, 2015).

Plant based dietary interventions have been suggested as alternative treatments to overcome metabolic disorders and obesity (Elhassaneen et al., 2017; Arabzadegan et al., 2020). For thousands of years, ginger (Zingiber officinale) was used widely as a food and an alternative medicine. It belongs to the family Zingiberaceae. Studies reported a lot of medicinal properties of ginger of which anti-obesity efficiency was the most cited (Tramontin et al., 2020). In general, ginger was found to combat weight gain through its thermogenic, lipolytic, anti-lipogenetic, fat absorption suppressive and appetite control properties (Ebrahimzadeh et al., 2018). These medicinal benefits are a result of a variety of phytochemicals. The most famous bioactive compounds in ginger include gingerol, zingerone, shogaol, paradols, and β-bisabolene (Kausar et al., 2021).

As a spice and a medicinal plant, ginger was used through this study to investigate its satiety stimulating and antihypothyroidic properties as mechanisms for its anti-obesity effect in female rats concurrently exposed to MSG.

Materials and Methods

Plant material: Dried ginger (*Zingiber officinale*) rhizomes were purchased from the local market for medicinal plants and herbs, Tanta city, Al-Gharbiyah governorate, Egypt. The herb was identified by the Department of Botany, Faculty of Science, Cairo University. The rhizomes were pulverized to a fine powder using a hammer mill (Thomas Willey mills, model Ed-5, Germany). After that, they were sieved with a screen of 80 meshper inch, stored in dry closed glass jars and kept at room temperature in the dark until used.

Chemicals and kits: Pure MSG (white colored crystals) was purchased from Sigma supplier in Cairo, Egypt. All other required chemicals were obtained from El-Gomhoreya Company for trading Drugs, Chemicals and Medical Appliances, Tanta City, Al-Gharbia Governorate, Egypt. Kits used for biochemical determinations were obtained from Gama Trade Company for chemicals, Cairo, Egypt.

Animals and study design: A total of 20 normal female albino rats (Sprague Dawley strain) were obtained from the animal colony, Helwan Farm, Vaccine and Immunity Organization, Cairo, Egypt. They were housed in well-aerated cages under hygienic conditions in a room maintained at suitable humidity, 22 - 25 °C and a 12 h light-dark cycle, and fed pelleted balanced diet purchased from Agricultural Development Company, 6-October City, Giza Governorate, Egypt. The diet was already consisting of sunflower oil (15%), concentrate mixture 45% (10%), yellow corn (49%), soybean meal 44% (11%), wheat bran (10%), molasses (3%), common salt (0.5%), ground limestone (0.2%), dicalcium phosphate (0.1%), lysine (0.2%), dl-methionine (0.7%) and mineral-vitamin premix (0.3%). By the end of the adaptation period (1 week), rats weighing 142 ± 28 g were divided into four groups of 5 rats each. The first group was kept as a negative control group, while groups from 2 to 4 were administered 6 mg MSG/kg body weight daily to induce obesity (Abdollahzadeh et al., 2017), with some modification as the administration was orally by a stomach tube and was not through intraperitoneal route. At the same time, group 2 was kept untreated (positive control), while the third and the fourth groups were fed pelleted balanced diet supplemented with 0.5 and 1% of ginger rhizomes powder (GRP), respectively. Rats received MSG and GRP all over the experiment (protective study). The experiment lasted for 6 weeks. Meanwhile, feed and water were provided *ad-libitum* and body weight was recorded once a week. By change of the body weight of each rat, its MSG dosage was also changed.

Sampling and treatment of blood and thyroid gland: By the end of the experiment, animals were weighed and fasted overnight before sacrificing. Blood samples were collected from the aorta of each rat into dry clean centrifuge tubes. Sera were carefully separated by centrifugation of blood samples at 3000 rpm (round per minute) for 10 minutes at room temperature, then transferred into dry clean tubes and kept frozen at -20 °C till analyzed. Moreover, thyroid was removed by careful dissection, washed in ice-cold NaCl (0.9 g/ 100 ml), dried using filter paper and divided

into two pieces. The first piece was homogenized in 9 vol of icecold potassium phosphate buffer (pH: 7.4) to obtain 10% homogenates, then cool centrifuged at 10,000 rpm for 15 min and stored in liquid nitrogen at -80 °C for further analyses. The second piece was immersed in buffered neutral formalin solution (10 % v/v) for latter histopathological examination.

Calculation of body weight gain, total feed intake and feed efficiency ratio: Body weight gain (BWG) was calculated by subtracting the initial weight of each rat from its final weight. Daily feed intake (FI/day) was calculated by subtracting the remainder feed for each animal from that allocated to it every day. In the same time, the wasted feed was weighed and subtracted. Total feed intake (TFI) was calculated through multiplying daily feed intake by 42. Feed efficiency ratio (FER) was then calculated through dividing BWG by TFI.

Hormonal assay: In sera, leptin and thyroid stimulating hormone (TSH) levels were measured using commercially available rat enzyme-linked immunosorbent assay (ELISA) kits, while triiodothyronine (T3) and thyroxine (T4) levels were determined using radioimmunoassay (RIA) kits.

Assessment of antioxidant/oxidant biomarkers in thyroid tissue homogenate: In thyroid tissue homogenate, the activities of both glutathione peroxidase (GPX) and catalase (CAT) were determined according to the methods described by **Paglia and Valentine (1967)** and **Cohen** *et al.* (1970), respectively, while the concentrations of both reduced glutathione (GSH) and the lipid peroxidation marker, malondialdehyde (MDA), were determined following the methods suggested by **Beutler** *et al.* (1963) and **Ohkawa** *et al.* (1979), respectively

Histopathological examination: Upon fixing in formalin solution at room temperature for 24 hours, thyroid tissue pieces were dehydrated in ascending grades of ethyl alcohol, cleared in terpineol and embedded in paraffin wax. Sections of 5 μ thickness were mounted and stained with Haematoxylin and Eosin (**Bancroft**

and Layton, 2013). All preparations were microscopically examined for the histopathological examination.

Statistical analysis: Statistical analysis was carried out using the program of Statistical Package for the Social Sciences (SPSS), PC statistical software (Version 20; Untitled – SPSS Data Editor). The results were expressed as mean \pm standard deviation (mean \pm SD). Data were analyzed using one-way classification, analysis of variance (ANOVA) test. The differences between means were tested for significance using Duncan test at p<0.05 (Sendcor and Cochran, 1979).

Results

Body weight gain, daily feed intake, feed efficiency ratio:

At the beginning, there were no significant differences in the body weight of all experimental groups, while at the end, marked differences were noticed. Thus, BWG of untreated MSG-administered group was found to be significantly (P<0.05) higher than that of negative control group. Supplementation of diet offered to MSG –administered groups with GRP (0.5 and 1%) resulted in a significant dose dependent decrease, however, neither the low concentration nor the high one could return BWG to its normal value (Table 1).

While FI/day was also increased significantly as a result of MSG administration, both concentrations of GRP (0.5 and 1%) could not reduce it significantly compared to untreated MSG-administered group. Like BWG, the mean value of FER was increased significantly due to MSG administration. While the two concentrations of GRP decreased FER significantly in a dose dependent manner, the high concentration was so efficient that led to no significant change compared to negative control group (Table 1).

administered versus control rats							
Groups	Negative control	MSG - administered	MSG - administered	MSG - administered			
Parameters			+ 0.5% GRP	+ 1% GRP			
Initial	138.35±17.62	139.12±17.72	135.40±18.74	144.00±18.56			
weight (g)							
Final	173.60±22.30 ^a	227.48±29.76 ^b	199.0±24.76 ^{ab}	192.70±24.49 ^{ab}			
weight (g)							
BWG (g)	35.25 ± 4.45^{a}	88.34 ± 11.36^{d}	$62.80 \pm 8.07^{\circ}$	48.70 ± 6.49^{b}			
FI/day (g)	15.60±1.99 ^a	20.16±2.55 ^b	19.54±2.45 ^b	19.07±2.39 ^b			
FER	0.05±0.01 ^a	0.11±0.02 ^c	0.08 ± 0.01 ^b	0.06±0.01 ^a			

Table 1: Effect of experimental diets supplemented with two concentrations of GRP on BWG, FI/day and FER in MSG - administered versus control rats

Results are expressed as mean \pm SD. Means with completely different superscript letters in each row differ significantly (P<0.05). MSG, monosodium glutamate; GRP, ginger rhizomes powder; BWG, body weight gain; FI/day, daily feed intake; FER, feed efficiency ratio.

Leptin and thyroid -related hormones:

In table 2, results revealed a significant reduction (P<0.05) in the mean values of both T3 and T4 in serum of untreated MSG – administered group compared to negative control group. Both 0.5 and 1% GRP –treated groups showed no significant elevation in T3 mean compared to untreated MSG –administered group, while only 1% GRP –treated group showed a significant increase in T4 mean. In contrast, serum levels of both leptin and TSH were significantly increased in untreated MSG –administered group compared to negative control group. Both 0.5 and 1% GRP –treated group. Both 0.5 and 1% GRP –treated groups recorded a significant decrease in TSH mean, with a significant decrease in the high concentration –treated group compared to the low concentration –treated one. As for leptin level, the two concentrations of GRP elevated it, however the elevation was not significant.

in sera of MSG -administered versus control rats						
Groups	Negative control	MSG - administered	MSG - administered +	MSG - administered		
Parameters			0.5% GRP	+ 1% GRP		
Leptin	6.00±0.75 ^a	6.78±0.83 ^b	6.80±0.81 ^b	$6.84\pm0.84^{\text{ b}}$		
(ng/ml)						
T3 (ng/ml)	0.88±0.11 ^b	0.51±0.06 ^a	0.53±0.07 ^a	0.58 ± 0.07^{a}		
T4 (ng/dl)	3.43±0.43 ^b	2.76±0.36 ^a	3.26±0.42 ^{ab}	3.35±0.43 b		
TSH	0.00 ± 0.00^{a}	$0.08\pm0.01^{\text{ d}}$	0.05 ± 0.01 ^c	0.02 ± 0.00 ^b		
(uIU/ml)						

Table 2: Effect of experimental diets supplemented with two					
concentrations of GRP on leptin and thyroid –related hormones					
in sera of MSG -administered versus control rats					

Results are expressed as mean \pm SD. Means with completely different superscript letters in each row differ significantly (P<0.05). MSG, monosodium glutamate; GRP, ginger rhizomes powder; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

Oxidative stress markers:

Findings in table 3 demonstrated that thyroid tissue homogenate of untreated MSG –administered group had a significant (P<0.05) higher level of the lipid peroxidation marker, malondialdehyde (MDA), compared to that of negative control group. In contrast, the level of reduced glutathione (GSH) and the activities of glutathione peroxidase (GPX) and catalase (CAT) were significantly decreased. Feeding MSG –administered groups on GRP –supplemented diets resulted in dose dependent improvement as MDA level was significantly lowered and a significant increase in GSH, GPX and CAT was noticed in thyroid tissue homogenates compared to untreated group.

 Table 3: Effect of experimental diets supplemented with two

 concentrations of GRP on oxidative stress markers in thyroid

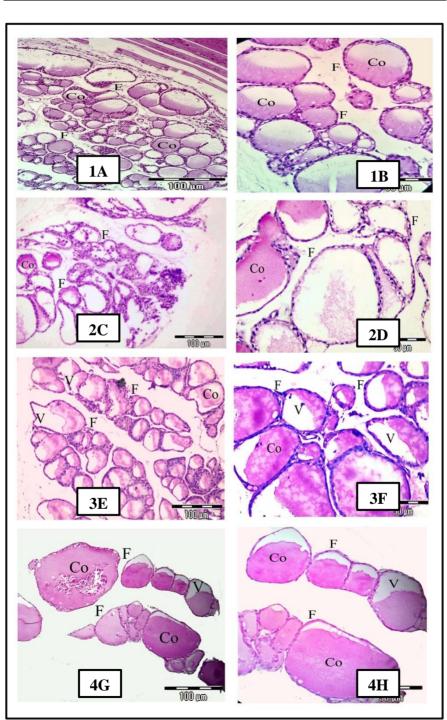
 tissue homogenates of MSG -administered versus control rats

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Groups	Negative control	MSG - administered	MSG - administered + 0.5% GRP	MSG - administered + 1% GRP	
Parameters					
MDA	72.67±9.91 ^a	172.83±21.66 ^d	135.10±16.86 ^e	106.3±13.58 ^b	
(nmol/g) GSH	1.86±0.22 ^d	0.44 ± 0.05^{a}	1.00±0.13 ^b	$1.40\pm0.17^{\circ}$	
GSH (mmol/g)	1.80±0.22	0.44 ± 0.03	1.00±0.15	1.40±0.17	
GPX (U/g)	470.40±59.61 ^d	133.97±16.43 ^a	286.46±35.47 ^b	379.48±47.66 ^c	
CAT (U/g)	4.79 ± 0.60^{d}	0.66 ± 0.09^{a}	2.25 ± 0.27^{b}	3.25±0.41°	

Results are expressed as mean \pm SD. Means with completely different superscript letters in each row differ significantly (P<0.05). MSG, monosodium glutamate; GRP, ginger rhizomes powder; MDA, malondialdehyde; GSH, reduced glutathione; GPX, glutathione peroxidase; CAT, catalase.

Histopathological findings:

Light microscopic examination of the thyroid gland of -ve control group showed normal thyroid architecture. In contrast, thyroid sections of rats from untreated MSG –administered group exhibited marked disorganization of thyroid structure. In a dose dependent manner, these histological abnormalities decreased to a large extent in GRP –received groups, as shown in the following photos:



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Photos 1A, 1B: Sections of the thyroid gland of control albino rats (group1) showing normal thyroid architecture; thyroid follicles (F) of variable sizes lined by cuboidal follicular cells with rounded nuclei, homogenous acidophilic colloid (Co) exhibiting peripheral small vacuoles. Blood capillaries and inter follicular cells can be seen between thyroid follicles. Photos 2C, 2D: Sections of the thyroid gland of rats from untreated MSG -administered group showing marked disorganization of thyroid structure; large distorted follicles with degeneration of its lining epithelia, absence of colloid and it is surrounded by a more or less continuous capillary network lined by endothelial cells. Presence of small distorted follicles with discontinuity of basement membrane lined by low to tall columnar cells. Follicular hyperplasia was detected in some follicles with multiple pyknotic nuclei. Photos 3E, 3F: Sections of the thyroid tissues of rats treated with MSG and 0.5% GRP showing thyroid follicles lined by short columnar epithelium with dark pyknotic nuclei and moderate amount of colloid in their lumina (Co) having some vaculation (V) in the cytoplasm of high cuboidal follicular cells (F). Photos 4G, 4H: Sections of the thyroid tissues of rats treated with MSG and 1% GRP showing nearly normal thyroid follicles with colloid in their lumina (Co), absence of pyknotic nuclei and few number of vacuoles (V) in the cytoplasm of high cuboidal follicular cells (F) (H & E X 200, 400).

Discussion

The present results revealed that MSG administration increased BWG, daily FI and FER. These results were in agreement with several previous studies (Gomathi *et al.*, 2008; Akataobi, 2020). Studies have shown that MSG can induce overweight through various mechanisms including its ability to induce hyperphagia and elevate the energy intake (Bergen *et al.*, 1998). Hyperphagia itself was found to be associated with MSG exposure due to improving palatability of food; as it is a taste enhancer, reduction of brain and plasma serotonin, and interruption in the hypothalamic signaling process of leptin which causes the exposed animal to eat more food while being hypoactive (Gomathi *et al.*, 2008; Roman-Ramos *et al.*, 2011).

On the other hand, results of the present study confirmed both the hyperleptinemic and leptin resistance promoting effects of MSG, which were previously supported by **Yuan** *et al.* (2014). Leptin, the product of the obese (ob) gene, is produced mainly by adipose tissues and plays a vital role in food intake regulation and energy expenditure (**Zhang** *et al.*, 1994). Herein, leptin resistance was confirmed by increasing feed intake in untreated MSG – administered group compared to the control one.

Rather than hyperphagia, other mechanisms may be involved in the weight gain stimulating effect of MSG (He *et al.*, **2008**). Functions of endocrines in general, and thyroid gland in particular, were found to be disturbed as a result of over and chronic MSG consumption. According to **Dong and Schneider (2013)**, MSG, in the present study, induced an overt hypothyroidic effect evidenced by increased level of thyroid stimulating hormone accompanied with decreased T4 level. In general, the hypothyroidic effect of MSG was in accordance with the findings of many previous studies, and can be attributed to the influence of MSG on hypothalamus-pituitary function and the secretion of hormones responsible for thyroid metabolism (**Nasir, 2019; Mekkawy et al., 2020; Dhindsa et al., 1981**).

The above mentioned effects of MSG on thyroid –related hormones can also be attributed to histopathological abnormalities occurred, in turn, due to stimulation of oxidative stress in thyroid tissue. Findings of the present work confirmed this suggestion as MDA, the lipid peroxidation marker, was increased significantly, while GSH level and the activities of the antioxidant enzymes, GPX and CAT, were lowered in thyroid tissue homogenate of untreated MSG –administered group compared to negative control group. Similar results were previously reported (**Nasir, 2019; Mekkawy** *et al.*, **2020**).

According to the present results, GRP, especially the high concentration, improved antioxidant defense system in thyroid tissue homogenate. As a result, structure abnormalities in thyroid tissue disappeared quietly and the sera concentrations of thyroid – related hormones were normalized. The anti-hypothyroidic properties of ginger rhizomes were in harmony with the results of many studies in which these effects were attributed to the antioxidant capacity evidenced by increasing antioxidant enzyme activities and decreasing lipid peroxidation in induced models of hypothyroidism (Al-Amoudi, 2018; Mohammed et al., 2020; Elgazwi et al., 2021). Not only hypothyroidism, but also its critical complications such as dyslipidemia was reported to be ameliorated by ginger extract administration (Al-Noorv et al., 2013). Concurrent exposure to Lambda-cyhalothrin, a widely used insecticide, and ginger aqueous extract led to an improvement in the

histological structure of the thyroid, with noticeable increases in glycogen and protein deposition as well as a significant reduction in DNA damage (Al-Amoudi, 2018). On the other hand, Mohammed et al. (2020) concluded that ginger extract was able to effectively protect against bisphenol A -induced thyroid oxidative damage by activating the Nrf-2/HO-1 gene expressions and enhancing the thyroid hormones synthesis. Within the thyroid tissues, downregulation of the Nrf-2/HO-I signaling is well known to eventually cause the DNA fragmentation. In general, the antioxidant effects of ginger rhizomes can be attributed to the presence of some bioactive compounds. Of them, shogaol was the most abundant and effective in the dried form (Bak et al., 2012). On the other hand, serum levels of some minerals including manganese and potassium were reported to be lower in hypothyroidic patients (Memon et al., 2015; Hemantha Kumara et al., 2016). The predominance of these micronutrients in ginger powder may be another cause for its antihypothyroidic effect (Ogbuewu et al., 2014).

Finally, the present study supports the potency of ginger rhizomes powder as an anti-obesity agent and attributes this potency to its anti-hypothyroidic effect and not to its satiety stimulating efficiency.

Conclusion

It could be concluded that the anti-obesity effect of ginger could be attributed to its anti-hypothyroidic properties, and not to satiety stimulation.

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ريزومات الزنجبيل كعامل مضاد للسمنة فى إناث الجرذان المعرضة لأحادي جلوتامات الصوديوم: التأثير المضاد لانخفاض نشاط الغدة الدرقية مقابل تحفيز الشبع كآليات محتملة

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يعد التعرض الزائد لمادة أحادي جلوتامات الصوديوم تحدي صحي كبير في مصر؛ وهكذا كان هناك حاجة إلى التدخلات الغذائية التي تستهدف الوقاية من الاضطرابات المرتبطة بهذه المادة المضافة وخاصة السمنة والتي حظيت وما زالت باهتمام كبير.

أجريت هذه الدراسة لبحث التأثيرات المحفزة للشبع والخافضة لنشاط الغدة الدرقية كآليات لتأثير الزنجبيل المضاد للسمنة في إناث الجرذان حيث تم استهلاكه بالتزامن مع التعرض لمادة أحادى جلوتامات الصوديوم. تم تقسيم ٢٠ جرذ أبيض بالغ إلى أربع مجموعات متساوية العدد تشمل المجموعة الضابطة، بينما تم تجريع المجموعات من الثانية إلى الرابعة بمادة أحادي جلوتامات الصوديوم (٦ ملجم/ كجم من وزن الجسم/ اليوم) وتركت دون معالجة مصاحبة (مجموعة ٢)، أو تم تغذيتها على عليقة مدعمة بمسحوق الزنجبيل بجرعتي قرم ٥. • ٥% ، ٢ ٥% (مجموعات ٣ ، ٤ على التوالي) لمدة ستة أسابيع. وفي النهاية، تم حساب الزيادة المكتسبة فى الوزن والمأخوذ الغذائي ومعدل كفاءة الغذاء، وتقدير هرمون الليبتن وهرمونات الغدة الدرقية في السيرم، في حين تم تقدير دلائل الأكسدة فى نسيج الغدة الدرقية. علاوة على ذلك تم فحص أنسجة الغداء الدرقية للجرذان هستوباثولوجيا. اقترن استهلاك مادة أحادي جلوتامات العرونيوم بحدوث زيادة في نسيج الغدة الدرقية. علاوة على ذلك تم فحص أنسجة الغدو

معززات النكهة.