

## The Effects of Orally Administered Monosodium Glutamate (MSG) on the Metabolic Syndrome of Adult Albino Rats

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### Abstract

Monosodium Glutamate (MSG) or glutamate is a commonly used flavour enhancer, naturally found in protein-rich foods; although produced commercially through the fermentation of molasses. MSG is essential in the metabolism of living bodies. The increase in MSG consumption has become a growing concern due to the lack of adequate data on its effects. This study investigates the effects of MSG on weight and blood glucose levels of adult albino rats for an experimental period of eight (8) weeks. Twenty-four (24) albino rats weighing between 48.7 g to 94.6 g were randomly divided into four (4) groups of six (6) rats each: 1 control group and 3 test groups. Test groups were fed and daily doses of MSG dissolved in water (8 g/L, 10 g/L and 15 g/L respectively) were administered orally. The control group were fed on plain water and rat chow (grower's mash) only. Weekly weights, fasting blood glucose levels of rats were measured, and change in behaviour and exploratory tendencies observed, all through the experimental period. Glycosylated haemoglobin was tested at the end of the experimental period to confirm the weekly blood glucose levels. There was no significant difference in the average weights ( $P > 0.05$ ). Blood glucose levels maintained a normal range of 4.5 – 5.1 % (good glycemic control) over the experimental period. The study illustrates that Monosodium Glutamate has no adverse effects on weight and blood glucose levels when consumed daily, but not exceeding a 15 g dose. Further research to validate casual inference may be necessary. The consumption of MSG should be in moderation and individuals prone to hypoallergenic reactions should ensure to check product labels for MSG before the consumption of foods. Further research can be carried out using higher doses as well as other metabolic markers in the body to further consolidate empirical data.

**Key Words:** Monosodium Glutamate (MSG), Weight, Blood Glucose Levels, *Diabetes mellitus*, Obesity

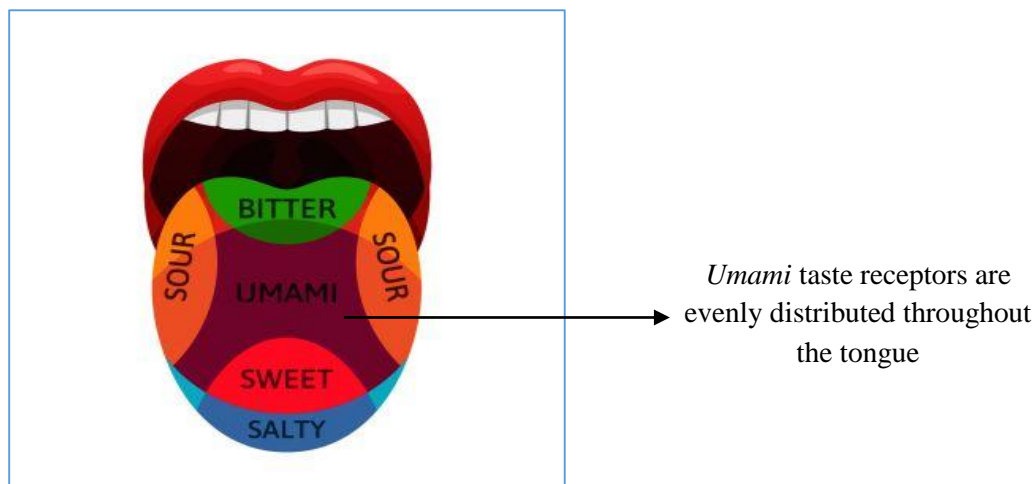
**Running Title:**MSG and Metabolic Syndrome

## Introduction

Monosodium Glutamate (MSG) commonly known as glutamate or glutamic acid is a flavour enhancer naturally found in tomatoes, mushrooms, parmesan cheese and many other protein-rich foods as well as fruits. It is also produced commercially through the fermentation of molasses. Glutamic acid occurs in two common forms. L-glutamic acid or 'protein bound' glutamic acid which is produced in natural foods and D-glutamic acid or 'free glutamic acid'. D-glutamic acid is artificially or chemically produced outside of the body and this is what is referred to as MSG. Glutamic acid is a non-essential Amino Acid (AA) and it plays an essential role in human metabolism. It is a substrate for protein production and plays a vital role in the transmission of nerve impulses. L-glutamic acid possesses both physical and chemical characteristics that makes it a key contributor

to the secondary structure of proteins ( $\alpha$ -helices). L-glutamate is synthesized from ammonia and  $\alpha$ -ketoglutarate in a reaction catalysed by L-glutamate dehydrogenase ( $\alpha$ -ketoglutarate transamination). This reaction is of fundamental importance in the biosynthesis of essentially all amino acids. MSG is a precursor of glutamine, an important neurotransmitter and also an energy source for certain tissues (intestinal tissues). It functions as an energy yielding substrate in the metabolism of dietary glutamate (Kaushalya and Jagath, 2017).

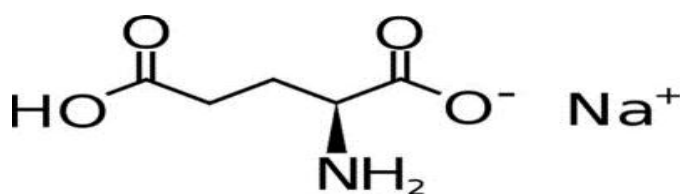
Commercially produced MSG is used as a chemical additive by food industries and is commonly marketed as a flavour enhancer (Lorell and Carbello, 2012). It gives a special savoury taste or palatability to processed foods known as "Umami" and also increases appetite.



**Figure 1:** Location of *Umami* Taste Receptors on the Tongue



**Plate 1:** Physical Appearance of Monosodium Glutamate



**Figure 2:** Chemical Structure of Monosodium Glutamate

The demand for Monosodium Glutamate around the world is estimated at more than three million metric tonnes which is valued at 4.5 billion Dollars (1.6 trillion Naira) with Africa being among the ten largest consumers in the world. According to the Institute for Human Studies (IHS) Nigeria, the global demand for MSG is expected to have increased by almost four percent annually between 2014 and 2019 to nearly 3.9 million metric tonnes. However the most significant increases in demand for this product will be in Thailand, Indonesia, Vietnam and China followed by Nigeria and Brazil (Xiong *et al.*, 2009, Oriaghan *et al.*, 2012).

Monosodium Glutamate is sold in most open market stalls and stores in Nigeria as “Ajinomoto” marketed by West African Seasoning Company (WASCO) Limited and as “Vedan” or “White Maggi” by Mac and Mei (Nig.) Limited. It is consumed as a food additive in both households and restaurants. MSG is used by consumer and institutional

food service providers, in animal feeds and in foods by food processing industries. MSG is largely used in the manufacture of seasoning cubes. A typical seasoning cube contains MSG, salt, sugar, extracts of vegetables and natural spices and flavours and/or extracts of poultry, fish or beef. The seasoning cube sector in Nigeria is a huge market because of the demand for this product, and it is estimated to be worth about Seventy Billion Dollars. This is almost the Gross Domestic Product (GDP) of some low- and middle-income countries (LMICs) of the world. Almost all the seasoning cubes in Nigeria contain MSG; it is sometimes presented under different names like: mono potassium glutamate, glutavene, glutacyl, glutamic acid, autolyzed yeast extract, Sodium Caseinate, E621 (E620-E632). Seasoning cubes are an indispensable composition of all Nigerian menus. It is thus safe to say that we all consume MSG in one form or the other, directly or indirectly (Michael & Peter, 2015).

**Table 1:** Concentration of MSG in Some Nigerian Seasoning Stock Cubes

Nigerian Seasoning	Monosodium Glutamate Concentration
Nestle Maggi	E621-E627
Royco	E621-E629
Onga	E620-E625
Ami Cubes	E620-E630
Doyin Cubes	E620, E621
Mr. Chef	E620- E623
Knorr	E621-E631
Tasty Cubes	E621

## Reference Ranges:

E620-E631: High concentration

E620-E630: High concentration

E621-E627: High concentration

E620-E625: Medium concentration

E620-E623: Medium concentration

E621: Low concentration

The acute consumption of Monosodium Glutamate has been associated with various forms of toxicity. It has been linked with obesity, metabolic disorders, neurotic effects as well as detrimental effects on the reproductive organs. Its chronic consumption, reportedly induces seizures, liver damage, brain damage and anemia (Oriaghanet *et al.*, 2012, Naizet *et al.*, 2018). Results from both animal and human studies have demonstrated that even the lowest dose of Monosodium Glutamate has toxic effects over time due to bioaccumulation. MSG reportedly disrupted neurones and may have had adverse effects on behaviour. Animal studies have demonstrated that neonatal MSG consumption sets a precedence for the development of obesity later on in the life of such an animal. Insulin resistance and reduced glucose tolerance in rodents due to MSG consumption has also raised concerns about the development of obesity in MSG-consuming humans (He *et al.*, 2015). It is also reported that Monosodium Glutamate consumption causes a disrupted energy balance by increasing the palatability of food and thus disturbing the leptin-mediated hypothalamus-signalling cascade; this has the potential of triggering obesity (Solomon *et al.*, 2015, Araujoet *et al.*, 2017). MSG also triggers micro-RNA expression of interleukin-6 (a cytokine protein that regulates lymphocyte function), tumour

necrosis factor, alpha-resistin and leptin in visceral adipose tissues. This leads to increased insulin, resistin and leptin concentrations in circulation and ultimately an impaired glucose tolerance which may potentially lead to the development of *Diabetes mellitus*. Studies have also demonstrated that MSG induces a significant decrease in liver transaminases indicating hepatic damage. This damage is likely as a result of non-alcoholic steatohepatitis which is often associated with a prolonged inflammation of the liver (Roman-Ramos *et al.*, 2011). The numerous arguments on the effects and safety of Monosodium Glutamate consumption in humans and animals, necessitates this research which was carried out to investigate the consequences of prolonged Monosodium Glutamate consumption at specified doses, using adult albino rats.

**MATERIALS AND METHODS***Experimental Animals*

Twenty four (24) seven weeks old Albino rats (*Rattus norvegicus domestica*), were obtained from the Animal House of College of Health Sciences, Benue State University, Makurdi, Nigeria. The rats were left to acclimatise for a period of two weeks with food and water only. The rats were pre-weighed and randomly divided into four groups

(Control, A, B and C) of six (6) rats each after the period of acclimatisation.

#### *Preparation and Administration of Monosodium Glutamate Solutions*

Monosodium Glutamate under the trade name *Ajinomoto* (99% pure MSG) was procured from a West African Seasoning Company (WASCO) accredited retailer at the Makurdi Modern Market in Makurdi Metropolis, Benue State, Nigeria. Approximated doses (15g/L, 10g/L and 8g/L) were completely dissolved in distilled water and administered orally to the test groups of experimental animals daily for eight (8) weeks respectively. Rat chow (grower's mash) and water were withdrawn daily by 12 noon and the animals starved for three hours before the oral administration of dissolved MSG. This was done to ensure adequate consumption of the MSG stock solution upon administration for a period of three (3) hours. Food and plain water was re-introduced to test groups after the 3 hour period. The control group was given only plain water and rat chow throughout the experimental period.

#### *Sample Collection and Laboratory Analysis Body Weights and Behaviour Patterns*

The weights of the rats in all test groups were measured three (3) times weekly for the entire duration of the experiment using an electronic weighing balance (Labtech BL 200L USA) and an improvised weighing cage. The mean weights were recorded in grams(g).

The rats were also observed daily for a duration of 12 hours to monitor change in behaviour and exploratory tendencies such as rearing, walling and appetite.

#### *Fasting Blood Glucose Test*

The animals were starved prior to sample collection for the purposes of this test. Using a sterile scalpel and a makeshift restraint, blood samples were obtained by making a cut on the tail vein of the animals and gently squeezing the tail to get two (2) drops of the blood. Fasting blood glucose levels were determined using a glucometer (ACCU-CHEK Active Roche Serial No: GU05959074, Mannheim, Germany) and glucose test strips (ACCU-CHEK Active Ref:07124112)

according to manufacturer's instruction. The process was repeated weekly for the entire duration of the experiment.

#### *Glycosylated Haemoglobin (Hb1Ac) Test*

This test was carried out at the end of the experimental period. The rats were anaesthetized using chloroform vapour and 5 ml of blood samples were collected via cardiac puncture and dispensed into EDTA tubes. The samples were subjected to a Glycosylated Haemoglobin test; carried out via a semi auto-analyzer (vitro scient) using the ion exchange resin method. 0.5ml of the lysing reagent was dispensed into tubes appropriately labelled as Test (T) and Control (C). 0.1 ml of the reconstituted control and well mixed whole blood samples were added into the 'T' and 'C' tubes respectively and properly mixed and allowed to stand at room temperature for 5 minutes to ensure complete lysis of the blood sample; this preparation is termed *haemolysate*. The ion exchange resin tubes were also labelled 'T' and 'C'; and 0.1ml of the haemolysate prepared was added to the appropriate ion exchange resins (T and C). A resin separator was inserted into each tube such that the rubber sleeve was approximately 1cm above the liquid level of the resin suspension. The contents of the tubes were mixed using a vortex mixer continuously for 5 minutes; and the resin allowed to settle. The resin separator was then pushed into the tubes until the resin was completely aspirated. Each aspirate was poured directly into a cuvette and their absorbance at 405nm was measured against distilled water. The total hemoglobin fraction was then determined by dispensing 2.5ml of distilled water into another set of tubes labelled T and C; 0.01ml of the haemolysate was dispensed in the labelled tubes and mixed properly. The absorbance of each was again read at 405nm against distilled water.

$$\text{Ratio of Test (Rt), was calculated as: } Rt = \frac{\text{Absorbance of test glycosylated haemoglobin}}{\text{Absorbance of total test glycosylated haemoglobin}}$$

$$\text{Ratio of Control (Rc) was calculated as: } Rc = \frac{\text{Absorbance of control glycosylated haemoglobin}}{\text{Absorbance of total test glycosylated haemoglobin}}$$

The Glycosylated haemoglobin was expressed in percentage as:

$$\frac{\text{Ratio of Test (Rt)} \times 10 \text{ (10 being the control value)}}{\text{Ratio of Control (Rc)}}$$

The reference range of the result was given as 8% in the manufacturer's guide.

### Statistical Analysis

The data obtained was analyzed using the analysis of variance (ANOVA) and differences between means were calculated

using Fisher's Least Significant Difference (FLSD);  $P < 0.05$ .

## RESULTS AND DISCUSSION

### Results

There was a progressive increase in the average weights of rats in the different treatment groups; this was evident in the second week of Monosodium Glutamate administration. However, statistical analysis confirmed there was no significant difference in their mean weights ( $P > 0.05$ ) over the course of eight weeks (Table 2).

**Table 2:** Mean Weights of Rats

Week	Control	A (15g/L)	B (10g/L)	C (8g/L)	F	P-value	LSD (5%)
1	76.35	56.90	70.43	58.37			
2	73.58	61.50	73.80	61.58			
3	79.07	64.48	64.48	66.78			
4	67.28	79.13	86.32	78.20			
5	90.62	82.98	92.95	88.77			
6	105.84	103.83	115.12	102.62			
7	106.66	114.36	118.33	107.65			
8	108.33	114.83	127.67	112.97	1.178	0.343	NS

$P > 0.05$

The behavioral changes in the test animals were hyperactivity which was majorly characterized by increase in free-standing rearing and walling, and an increasingly voracious appetite.

Fasting blood glucose levels and glycosylated haemoglobin test results

demonstrate that the blood glucose levels of the test rats increased significantly ( $P < 0.00$ ) but maintained a healthy range of 4.5 – 5.1 %, indicative of a good glycemic control. Test group B had the best glycemic control of 4.5 % (4.6 mmol/L) within the three test groups of the experiment (Table 3 and 4).

**Table 3:** Average Fasting Blood Glucose Levels of Rats

Week	Control	A (15g/L)	B (10g/L)	C (8g/L)	F	P-value	CV (5%)
1	82.50	88.01	81.01	94.76			
2	82.50	88.22	82.45	94.80			
3	82.50	89.12	82.63	102.24			
4	82.32	90.13	78.80	102.01			
5	82.41	90.00	80.22	104.72			
6	82.33	89.01	82.33	99.60			
7	82.50	88.13	80.14	99.60			
8	82.50	88.22	82.50	99.99	7.642	0.000**	19.52

$P < 0.05$

**Table 4:** Glycosylated Haemoglobin After Treatment with MSG

Treatment groups	Hb1Ac (%)	Mean blood glucose(MBG) mg/dl	Estimated average glucose(eAG) mmol/L
Control	4.5	82.5	4.6
A(15g/L)	4.7	88.2	4.9
B(10g/L)	4.5	82.5	4.6
C(8g/L)	5.1	99.6	5.5

Reference range:

5.5 - 6.4 : Good glycemic control

6.5 - 7.9: Fair glycemic control

≥ 8.0 : Poor glycemic control

### Discussion

The consumption of healthy and nutritious food is essential to life. The palatability of food plays an important role in its consumption; thus the usual practice all over the world to amplify the taste and flavour of foods by means of food enhancers and additives. One of such commonly used being Monosodium Glutamate (MSG). Organically prepared and processed foods alike are enhanced with MSG in its pure or modified form. Food prepared with MSG always has the characteristic *Umami* taste and other typical flavours imparted by MSG. However, when enhancing palatability, it is of paramount importance to ensure that food additives will not cause harm to consumers. The safety of Monosodium Glutamate consumption and its acceptable doses has been reviewed extensively in the last twenty years by several regulatory organizations and expert bodies backed by data from empirical studies (Cynober *et al.*, 2018; Roberts *et al.*, 2018). These research findings still leave room for further studies hence this research. It is important to note that just like this study, the majority of research done has been on experimental laboratory animals and not on human test subjects thus the results of some of such studies may not be readily transferable to humans.

The three doses of MSG used in the present study did not register any significant change in body weight (Table 2). The study demonstrated that Monosodium Glutamate at the doses 15g/L, 10g/L and 8g/L administered had no significant effects on weight gain

( $P > 0.05$ ). These results corroborate with findings by Maluly *et al.*, (2013) who reported that ingestion of MSG had no effects on body weight gain however it deviates at the point of food consumption in albino rats as an increasingly voracious appetite was reported by the present study. Tordoff *et al.*, (2012) also reported that MSG did not influence body weight or energy levels in adult rats and mice. This report varies slightly with the present study at the point of energy levels as hyperactivity which was mainly characterized by increase in free-standing rearing and walling was reported by the present study. The findings of Miskowiak and Partyka (2010) and Merrett (2009) also illustrate that MSG consumption has little or no effects on weight gain when consumed at certain doses. The findings of the present study however are not in tandem with the findings of Abd *et al.* (2014) who reports that MSG was found to cause a significant increase in the body weight and food consumption of animals fed with 4 g/L of MSG and similarly Hermanussen *et al.* (2009). El-Helbaway *et al.* (2017) demonstrates a significant increase in body weight of neo-natal albino rats exposed to 10 g/L Monosodium Glutamate. Nosseir *et al.* (2012) reports that through the stimulation of orosensory receptors, MSG influenced the appetite positively, thus induced weight gain. Nosseir *et al.* (2012) also reports that there was a significant reduction in the body weight after a recovery period of 6 weeks cessation of MSG indicating that the effects of MSG on body weight is temporary. Afifi and Abbas (2011) also report a significant spike in the abdominal

fat and general body weight in the offsprings of MSG-fed albino rats; thus classified as obese. They argued that the parent rats also fed on high-calorie chow and this could possibly play a role in the weight gain. Rats on leaner rat chow also exhibited weight gain but not significantly. This indicates that the effects of MSG on body weight gain may be greatly influenced by the type of diet. The rats of the present study fed on a low-calorie diet. It is noteworthy that most of the studies that have reported MSG as unsafe for consumption were carried out on immature rodents and neonates metabolise MSG differently.

He *et al.* in a 2011 study argues that a 1.6 to 2.2 g/d in-take of MSG did affect the Body Mass Index (BMI) of adult humans. Their research though by casual inference, reports that MSG is positively and longitudinally associated with overweight development among apparently healthy Chinese adults. A similar study conducted on humans by Hien *et al.* (2013) in Vietnam presents different findings. It reports that an average daily in-take (ADI) of Monosodium Glutamate (2.2g), did not increase the weights of test subjects. Similarly, Boutry *et al.* (2011) had reported that long term administration of MSG does not increase food in-take or induce obesity. In humans, Glutamate consumption by suckling babies via their mothers' milk is seen as beneficial for physiological support of growth due to its central role in the process of transamination; thus the encouragement that nursing mothers consume MSG at permissible levels (Ashaolu *et al.*, 2011). This present study is suggesting that the average daily in-take of MSG even in humans could be 15 g. Humans and rodents share similarities in metabolism hence the relatability of this dosage.

Hyperglycemia is indicated by elevated blood glucose levels for prolonged periods. It is a dangerous metabolic disorder as it can damage the vessels that supply blood to vital organs, thus increasing the risk of heart disease, stroke, kidney disease, vision problems, nerve problems and ultimately death. Persistent

hyperglycemia is termed *Diabetes mellitus* (Type I, Type II or Gestational) and medical practitioners opine that early diagnosis and management can avert and/or control the deleterious effects of this metabolic disorder, frequent and regular checks are strongly encouraged. *Diabetes mellitus* could be hereditary (Type I) or develop as a result of poor lifestyle and diet choices (Type II) or develop during pregnancies and last a life time (Gestational diabetes). The increasing number of elderly people in the world, and a high prevalence of obesity and sedentary lifestyles has pushed the incidence and prevalence of *Diabetes mellitus* to near epidemic levels (Igile *et al.*, 2013, Hossam, 2014).

The Glycosylated Haemoglobin Test (HBA1c) helps to determine the estimated average blood glucose (eAG) over a period of time. Haemoglobin, the oxygen-carrying component of the blood, forms aHBA1-complex with glucose when present in blood. The higher the blood glucose levels, the higher the availability of this complex in blood. Red blood cells survive an average period of 120 days in blood as such a measure of this complex gives an overview of the glucose present in the body over a period of 90 to 120 days; hence the principle of this diagnostic test. The Glycosylated Haemoglobin Test results of the test rats after the experimental period revealed that the administration of MSG did not affect the blood glucose levels of the test groups adversely as they maintained a good glycemic control within a range of <8.0 mmol/L. This corroborates the results of the Fasting Blood Glucose Test performed weekly on the test albino rats for the duration of the experimental period (Table 3 and 4). This is in agreement with the findings reported in similar studies. Abdulsalam *et al.* (2018) also observed no changes in insulin levels or glucose tolerance during MSG supplementation. They argue that the functional blood glucose impairment may require a second hit or a separate factor for susceptibility. Hugues *et al.* (2009) reports that



high doses of 20g and 30g of MSG had no significant effects on the blood glucose levels (4.73 and 6.25mmol/L respectively). Boonate *et al.* (2015) reports same but for a lower dose of 2.0 g/d.

The findings of Oriaghan *et al.* (2012) however disagree with the findings of the present study. Oriaghan and associates in a similar study carried out in Edo State, report an increase in the blood glucose levels of adult rabbits orally administered with 3.3g and 6.6g of MSG. Oriaghan *et al.*, also reports that, asides an increase in plasma insulin concentration, there was continual increase in plasma glucose levels in the MSG-treated groups from the third week till the completion of the duration of experiment. This corresponds with findings from other similar studies where significant increase in plasma glucose levels was reported with MSG altering the regulatory mechanisms that affect fat metabolism, resulting in the propensity for creating adipose tissue and the weakening effect of fats on insulin action. The disparity could be attributed to the difference in choice of experimental animals (Boutry *et al.*, 2011, He *et al.*, 2015, Araujo *et al.*, 2017). The results from this present study also disagree with a study conducted by Ogbuagu *et al.* (2015) who reports a significant increase in body weight and fasting blood glucose levels of MSG-treated albino rats. The oral administration of a 24 g MSG dose increased fasting blood glucose levels and body weight faster than a 12 g dose ( $P < 0.05$ ). This study also associates head trauma and tenderness of the pericranial muscles of the albino rats to MSG administration.

The similarities and differences in findings could be casually attributed to the similar or varying environmental factors in the diverse experimental locations (the present study was carried out in Makurdi, Benue State, Nigeria), duration of experimental periods, doses administered and the methods of administration.

### Conclusion

This study illustrates that Monosodium Glutamate has no significant effect on weight

and blood glucose levels even when consumed daily. Daily consumption however must not exceed a limit of 15 g. Further research is however needed to validate casual inference.

The findings of this study thus form the basis of the following recommendations:

- i. Monosodium Glutamate should be consumed in moderation, a limit of 15g per day is advised.
- ii. The use Monosodium Glutamate by Food processing industries/companies should be regulated to ensure that only non-toxic dosages of MSG are used in their products.
- iii. Further research can be carried out using higher doses as well as other metabolic markers in the body to further consolidate empirical data. This can also be done using human test subjects rather than animal test subjects.
- iv. People who are sensitive to flavor enhancers especially Monosodium Glutamate should check food labels of processed foods for MSG or codes that represent MSG, before consumption of such foods.

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