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Effects on Blood Urea Nitrogen (BUN) Levels in Pregnant White Rats (*Rattus norvegicus*) Following Administration of Organic and Synthetic Monosodium Glutamate (MSG)

ABSTRACT

High doses of MSG are associated with oxidative stress and metabolic kidney damage, raising concerns about long-term use. While the WHO reaffirms the safety of MSG (120 mg/kg BW), there is limited research on the long-term effects of MSG, especially at different levels of consumption. The aim of this study is to determine the levels of urea or BUN in rats exposed to synthetic MSG and liquid organic MSG. Control group (C): normal chow only. Treatment groups (T1-T6): The doses of organic or synthetic MSG administered were 60 mg/kg bw, 120 mg/kg bw and 240 mg/kg bw for 19 days. No significant differences in BUN levels were observed between the control and treatment groups ($p > 0.05$). The highest BUN levels were found in the control group, while the lowest levels were found in the group receiving the highest dose of synthetic MSG (240 mg/kg BW). Organic MSG (120 and 240 mg/kg BW) showed lower BUN levels compared to the 60 mg/kg BW dose, suggesting potential renoprotective effects due to the bioactive compounds present in tempeh and pineapple bromelain. Synthetic MSG at 240 mg/kg BW resulted in the lowest BUN levels, but this may reflect reduced protein intake or other metabolic adaptations rather than safety. The research highlights the potential of organic MSG as a safer alternative to synthetic MSG, particularly for renal health. However, long-term consumption of MSG, even at moderate levels, may still pose risks, highlighting the need for further research to establish safe consumption limits.

Keywords: health risk, healthy lifestyle, non-communicable disease

INTRODUCTION

Over the past decade, fast food consumption has increased significantly. As many as 65% of people habitually consume fast food at least once a week, with 13% of them consuming it daily [1]. Millennials have the highest frequency of fast food consumption, indicating that fast food has become a staple [2]. The convenience of fast food is the choice of people today, including in determining food preferences between busy social demands, including the affordable price of fast food, its social aspects, effective marketing strategies and evolving tastes. Fast food, which is low in fibre but high in energy, reflects a shift towards convenience and fast food solutions [3]. The appeal of fast food is linked to adding a wide variety of flavourings and other additives to create flavours that appeal to consumers [4].

Monosodium glutamate or MSG is one of the most widely used flavour enhancers, known for its ability to impart a savoury taste, often referred to as umami [5,6]. MSG is derived from glutamic acid, an amino acid found in many foods [7]. For example, in high-protein foods such as beef, pork, poultry, fish, and shellfish, then in cheeses such as Parmesan and Roquefort, various vegetables such as tomatoes, mushrooms, broccoli, and in milk [8,9]. Since its discovery 100 years ago by Kikunae Ikeda, the use of MSG has continued to increase year on year [10] growing over the decades from around 200,000 tonnes per year in 1969 to around 3 million tonnes per year currently consumed globally [11,12]. This increase reflects the growing demand for MSG as a flavour enhancer in various cuisines and processed foods.

The debate on the safety of MSG is rooted in historical misconceptions and evolving scientific evidence [9]. While the World Health Organization (WHO) affirms its safety for moderate consumption at 120 mg/kg BW, ongoing discussions about its potential health effects continue to shape public opinion [13]. Further research is needed to address remaining concerns about the health effects of MSG, particularly at different levels of consumption.

Several studies have indicated that high doses of monosodium glutamate (MSG) can adversely affect kidney health, primarily through oxidative stress and subsequent structural alterations in kidney tissue, including glomerular shrinkage and tubular degeneration. These alterations are indicative of early kidney damage. Oxidative stress is linked to elevated levels of reactive oxygen species (ROS) and reduced activity of antioxidant enzymes, resulting in cellular damage and compromised renal function [14,15,16]. It also disrupts metabolic pathways in the kidney, leading to electrolyte imbalances and modified excretion of metabolites such as trimethylamine N-oxide (TMAO). Elevated levels of TMAO have been associated with kidney damage and other systemic health issues [17,18]. While some studies propose that moderate consumption may not present a significant risk, long-term high consumption seems to be detrimental [14,15,17].

These adverse effects are caused by similar types of monosodium glutamate (MSG) on the market. So a new alternative is needed to replace the role of MSG in the market, usually called synthetic MSG. There are already several organic MSGs on the market, but most of them still contain high levels of salt when you look at their composition. The high sodium content means more toxins for the kidneys to filter out. Another solution is MSG made from tempeh protein with pineapple bromelain, which produces a hydrolysate. The innovation of using tempeh hydrolysate with pineapple bromelain extract is a promising step in the development of an organic liquid MSG alternative. This approach may address health concerns associated with synthetic flavour enhancers and high salt content [19].

One of the alternative raw materials for this organic MSG is tempeh, which has a high protein content of around 18-20g/100g [20]. This high number is very important for repairing damaged cells and supporting overall body function, including kidney function. In addition, the potassium content of around 367mg/100g regulates fluid balance in the body and reduces pressure on the kidneys [21]. Then, the use of bromelain in pineapple can reduce pro-inflammatory compounds such as INF-g and INF-γ and provide a decrease in urea and creatinine levels [22,23]. However, the effect of synthetic MSG on increasing urea or BUN with organic MSG from tempeh with pineapple bromelain also remains to be investigated. Therefore, this study aims to determine the levels of urea or BUN in white rats (*Rattus norvegicus*) exposed to synthetic MSG and liquid organic MSG.

METHODS

This study used multiple groups for the completely randomised design (CRD) experiment and the post-test-only control design. There were seven experimental groups in total, namely Control Group

(C): rats were given normal chow only; Treatment Group 1 (T1): rats were given organic MSG at 60 mg/KgBB orally for 19 days retrieved from [24]; Treatment Group 2 (T2): rats were given organic MSG at 120 mg/KgBB orally for 19 days (WHO recommended safe limit, 2018); Treatment Group 3 (T3): rats were given organic MSG at 240 mg/KgBB orally for 19 days retrieved from [24]; Treatment group 4 (T4): rats were given synthetic MSG at 60 mg/KgBB orally for 19 days retrieved from [24]; Treatment group 5 (T5): rats were given synthetic MSG at 120 mg/KgBB orally for 19 days (WHO recommended safe limit, 2018); Treatment group 6 (T6): rats were given synthetic MSG at 240 mg/KgBB orally for 19 days retrieved from [24]. Doses of MSG, both organic and synthetic, are certainly adjusted to the rat dose.

After 13 days of treatment, 1.5 mL of blood was collected from each rat via the orbital sinus after 12 h of fasting and stored in microtubes without anticoagulant. The treatment of white rats (*Rattus norvegicus*) was performed at the Laboratory of Animal Experiment Medicine, Sebelas Maret University, where all animals were kept under the same conditions, with a temperature of $23 \pm 2^{\circ}\text{C}$ and a 12-hour light/dark cycle.

Ethical Approval

This study was approved by the Health Research Ethics Committee, Faculty of Health Sciences, University Muhammadiyah Surakarta, and declared ethically feasible according to 7 (seven) WHO standards 2011 with number 351/KEPK-FIK/V/2024.

Monosodium Glutamat (MSG)

Organic MSG is given in liquid form, made from the hydrolysate of tempeh with pineapple bromelain in a ratio of 1:1.5 (Wicaksono et al, 2025). Synthetic MSG, on the other hand (Monosodium glutamat Merck Co., AS CAS No. 6106-04-3), is supplied as a crystalline powder that dissolves rapidly in water. Both monosodium glutamate were dissolved in distilled water and then orally injected into the mother rats, and the dose for each rat was determined based on its body weight.

Statistical Analysis

The data analysis technique of this study used the one-way Anova test using SPSS version 22 with the requirement of normality test using Kruskal-Wallis with the provisions if the $p\text{-value} > 0.05$ then the data can be said to be normally distributed (Riwidikdo, 2012). Then, after the homogeneity has been proven, the data analysis stage continues. Data can be considered to have equal variance or homogeneity if the $P\text{ value} > 0.05$. Experimental designs with more than 2 designs were tested with the one-way ANOVA test ($p < 0.05$).

RESULTS AND DISCUSSION

Comparison of normal BUN levels in rats with those obtained after 13 days of MSG administration, both organic and synthetic, showed that there was no significant difference ($p > 0.05$). Comparison of the groups after the 13-day experimental period showed that the untreated group of rats had slightly higher BUN levels than the other groups, which was not significant. The lowest BUN levels were observed in rats given a high dose of synthetic MSG at 240 mg/kg bw. When comparing normal creatinine levels, all rats in the different groups had high serum creatinine levels, which did not show a statistically significant difference ($p > 0.05$) at the end of treatment. In contrast, the BUN level of the highest treatment group was found in rats administered a high dose of synthetic MSG at 240 mg/kg bw. The results are summarised in Table 1.

Table 1. Mean BUN values of rats given organic and synthetic MSG

Treatment Group	BUN Values (mg/dl) (Mean $\pm$ SD)
C	26,275 ^a $\pm$ 3,4169
T1	26,025 ^a $\pm$ 5,6169
T2	25,3 ^a $\pm$ 4,9255
T3	25,3 ^a $\pm$ 0,8756
T4	25,35 ^a $\pm$ 2,2546

T5 25,25^a ± 5,4323

T6 23,025^a ± 3,2847

Superscript indicates significant difference ($p < 0.05$). Group C received distilled water by gavage for 13 days. Group T1 received organic MSG 60 mg/kg bw by gavage for 13 days. Group T2 received organic MSG 120 mg/kg bw by gavage for 13 days. Group T3 received organic MSG 240 mg/kg bw by gavage for 13 days. T4 received 60mg/kg BW by oral gavage for 13 days. Group T5 received synthetic MSG 120 mg/kg bw by gavage for 13 days. Group T6 received synthetic MSG 240 mg/kg bw by gavage for 13 days.

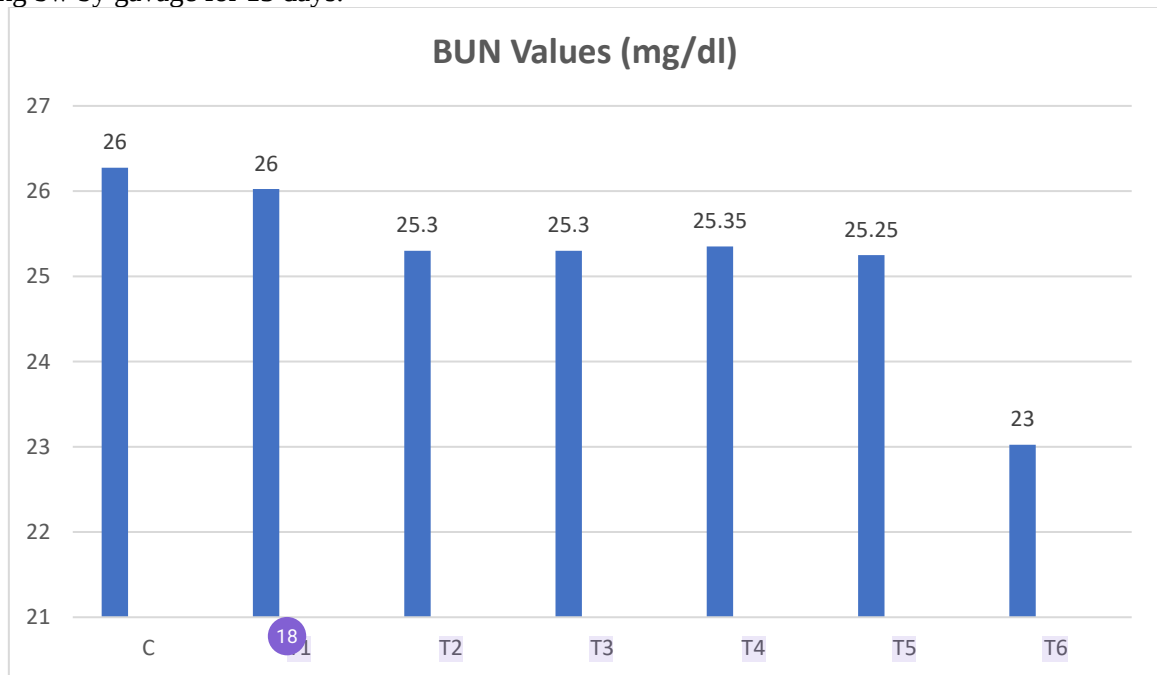


Figure 1. Table comparing the results of serum BUN levels after MSG administration. Group C was given distilled water by oral gavage for 13 days. Groups T1-T3 each received an oral dose of 60, 120 and 240 mg organic MSG/kg body weight for 13 days. Groups T4-T6 each received an oral dose of 60, 120 and 240 mg synthetic MSG/kg body weight for 13 days.

This study was designed to evaluate the effects of administering organic and synthetic monosodium glutamate (MSG) on serum blood urea nitrogen (BUN) levels in rats. Results showed was no significant difference ($p > 0.05$) in serum BUN levels between treatment groups. The control group (C) had a BUN level of 26.275 ± 3.4169 mg/dl. The groups receiving organic MSG (T1, T2, T3) had slightly lower BUN levels, 26.025 ± 5.6169 mg/dl, 25.3 ± 4.9255 mg/dl and 25.3 ± 0.8756 mg/dl, respectively. Meanwhile, the group receiving synthetic MSG (T4, T5, T6) also showed a decrease in BUN levels with values of 25.35 ± 2.2546 mg/dl, 25.25 ± 5.4323 mg/dl and 23.025 ± 3.2847 mg/dl, respectively. Cellular damage was evident in the elevated BUN levels. However, all groups observed had BUN levels above normal rat levels, which should be expected.

These results indicate that administration of MSG, both organic and synthetic, can affect serum BUN levels in rats. The significant difference between the control and treatment groups suggests that MSG has some effect on nitrogen metabolism in the body. Further research is needed to understand the mechanism underlying this effect and its health implications.

Discussion

The role of monosodium glutamate (MSG) as a flavour enhancer is almost irreplaceable, especially in Asia-Pacific countries. MSG itself has two effects in food, namely as an inducer of the unique flavour 'umami' and as a flavour enhancer that makes food taste delicious [6]. To date, the daily intake limit for MSG is still around the WHO recommendation of 120 mg/kg BW, but long-term daily intake has not been established [25,26]. Although some studies may address tolerance levels close to this range, regulatory agencies and scientific consensus generally advise against exceeding certain thresholds due to potential adverse effects. Doses above 85.8 mg/kg are associated with headache and doses above 150 mg/kg may cause an increase in blood pressure. There was a significant reduction in sperm quality and changes in the reproductive organs in male rats at 120

mg/kg bw. Due to the presence of glutamate receptors, the reproductive system appears to be particularly susceptible to glutamate-induced damage. MSG caused significant liver damage in adult Wistar rats at doses of 0.04 g/kg and 0.08 g/kg. Histological changes included central venous dilatation and degenerative changes in hepatocytes [9, 27,28].

Many studies have shown that dietary factors, including MSG, are associated with the risk of kidney disease. The chronic consumption of MSG can cause damage to the kidneys, mainly through the mechanism of oxidative stress. Studies in animals have shown that the ingestion of MSG can induce oxidative stress, leading to renal toxicity characterised by a decrease in the activity of antioxidant enzymes and an increase in lipid peroxidation. [14,29]. MSG with a high-fat, high-fructose diet exacerbates renal injury and alters the gut microbiota, leading to the risk of chronic kidney disease (CKD) [30]. It also causes the formation of kidney stones due to urine alkalinisation, which can predispose to obstructive nephropathy [14].

All groups of rats had elevated serum BUN levels compared with normal levels in healthy rats (Table 1). Normal rat BUN levels of 15-22 mg/dL are resistant to age- and sex-related variations [31,32]. Blood urea nitrogen (BUN) levels in pregnant rats do not change significantly from day 16 to day 19 of pregnancy [33]. Surprisingly, BUN levels were highest in rats fed only distilled water and normal chow (K). This may be because the type of diet and hydration status have a significant effect on BUN levels. Rats given only distilled water may experience different metabolic processes compared to rats given a varied diet, which may lead to elevated BUN levels due to decreased renal function or altered nitrogen metabolism [34,35]. In a study comparing distilled water with reduced natural water, rats given distilled water had higher BUN levels (28.2±9.0 mg/dL) than those given reduced natural water (22.9±9.3 mg/dL) [36]. This suggests that the type of water consumed can have a significant effect on BUN levels.

The group treated with organic MSG at a dose of 120 and 240 mg/kg body weight had low BUN levels compared with the rats given a dose of 60 mg/kg body weight, although they were still high compared with normal levels. There are several influencing factors, such as the raw materials used to make organic MSG from pineapple and soy tempeh. Research has shown that daily consumption of pineapple can reduce BUN levels. A study of rats fed a cholesterol-rich diet found that pineapple consumption over an 8-week period reduced BUN values, indicating that pineapple may protect renal function and possibly improve renal health [37]. Furthermore, pineapple bromelain has been shown to have anti-inflammatory effects through modulation of inflammation mediators. This effect may be beneficial in conditions that cause elevated BUN levels due to inflammation or renal stress [38,39]. Tempeh is rich in bioactive compounds and antioxidants that may help reduce oxidative stress, a contributing factor to renal dysfunction. By reducing oxidative stress, tempeh has the potential to lower BUN levels by improving overall renal function and filtration capacity [40]. Tempeh and bromelain (a pineapple enzyme) have been studied for their potential benefits to kidney health and their effect on blood urea nitrogen (BUN) levels. Tempeh may help stabilise BUN levels because its protein is easily metabolized and does not stress the kidneys. However, excessive consumption of protein from tempeh can still increase BUN if it exceeds the filtration capacity of the kidneys. Meanwhile, bromelain from pineapple may help lower BUN levels by increasing the efficiency of protein metabolism and reducing the accumulation of nitrogenous waste in the blood. The combination of tempeh and bromelain may provide synergistic benefits for renal health, helping to maintain renal function and stabilise BUN levels.

Unexpected results in the synthetic MSG group BUN was near normal until the highest synthetic MSG dose of 240 mg/kg bw had the lowest BUN. The administration of MSG at a high dose of 1,500 mg/kg body weight resulted in a statistically significant increase in the serum urea level in comparison with the control group. Lower doses (500 mg/kg and 1000 mg/kg) however did not result in significant changes in BUN, suggesting that the effect of MSG on BUN is dose dependent [41]. Higher levels of MSG (up to 1600 mg/100 g body weight) caused an increase in serum urea levels after 14 days of treatment. This suggests that excessive MSG consumption may negatively affect renal function and lead to increased BUN levels [42,43]. Several studies have monitored BUN levels in pregnant rats at different stages of pregnancy. The results showed that BUN levels tended to increase as pregnancy progressed. This increase is attributed to increased protein metabolism and changes in renal function during pregnancy. Pregnant rats fed a high-protein diet had higher BUN levels than pregnant rats fed a normal [44].

Low BUN levels in the 240 mg/kg BW synthetic MSG treatment group (T6) may indicate that pregnant rats experience a decrease in dietary protein intake. BUN is the end product of protein

metabolism, so low protein intake will reduce urea production. A decrease in BUN levels due to a low protein diet may indicate nutritional deficiencies that may affect fetal growth and maternal health [44]. However, a decrease in BUN in this case is a normal physiological response to pregnancy and does not necessarily indicate a health problem [33]. It should be noted that a decrease in BUN and liver dysfunction may indicate a serious problem that requires further evaluation [45]. Decreased BUN levels in pregnant rats can be caused by a variety of factors, ranging from normal physiological changes during pregnancy to pathological conditions such as liver disease, malnutrition or infection. It is important to evaluate the cause of the decrease in BUN in the context of the study, including diet, health status, and stage of pregnancy. If the decrease in BUN is accompanied by other symptoms or changes in biochemical parameters, further evaluation is required to determine the exact cause.

However, it is important to note that long-term exposure or higher doses could potentially alter these markers over time [46,47]. Therefore, continuous monitoring and comparison with baseline measurements is essential to assess overall renal health and metabolic status in experimental settings. By comparing these observations with standard reference ranges, researchers can conclude that while there may be slight variations that indicate mild stressors or adjustments in metabolic processes, none of the parameters strongly suggest adverse effects on renal function at this particular dose and duration of exposure. Further research focusing on long-term effects will provide more definitive insights into the safety limits and therapeutic window for similar treatments.

The findings of this study indicate that there is no significant difference between the groups, which is also influenced by the duration of exposure, the treatment for 13 days being included in the category of short-term exposure (acute) [48]. Including the mother rat, the body is still able to compensate for the toxic effects of MSG in a short time [49], so that BUN levels remain stable. Although 13 days may seem short, damage to kidney tissue or other organs may have already occurred, especially if the dose of MSG administered is high enough. This damage is probably not so serious as to have a major impact on the BUN value. Therefore, other parameters such as renal histopathology, creatinine levels or oxidative stress markers may be more sensitive in detecting early tissue damage.

MSG has a vital role in the food industry as a taste enhancer, but its use requires careful monitoring because of the potential for adverse health consequences. This study shows that BUN levels and renal function in rats can be affected by the consumption of MSG, both organic and synthetic. Although some treatment groups showed lower BUN levels, this does not necessarily indicate that MSG is safe for long-term consumption. In determining the health effects of MSG, factors such as dosage, type of ingredients and duration of consumption play an important role. To understand the mechanisms underlying the effects of MSG and to establish safe limits for long-term consumption, more research is needed. This will allow more appropriate recommendations to be made to ensure the safe consumption of MSG in the daily diet.

CONCLUSION

This study concluded that BUN decreased with increasing dose of both organic and synthetic MSG in white rats (*Rattus norvegicus*). At certain doses of organic MSG (120 and 240 mg/BW), BUN levels may be stable in pregnant rats. The administration of synthetic MSG also reduced the level of BUN, although this was not significant in the pregnant rats.

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