|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article
Volume 4, Issue 4; April: 2020; Page No. 107-111

THE INFLUENCE OF WATERMELON (*CITRULLUS LANATUS)* JUICE INTAKE ON THE KIDNEY OF WISTAR RATS (*RATTUS NOVERGICUS*) EXPOSED TO MONOSODIUM GLUTAMATE

S Mulyani[1], N Meutia[2*] and Sufitni[3]

[1]Magister Biomedic, Faculty of Medicine, Universitas Sumatera Utara Jl. Dr. Mansyur No.5 Medan 20155, Indonesia

[2]Department of Physiology, Faculty of Medicine, Universitas Sumatera Utara Jl. Dr. Mansyur No.5 Medan 20155, Indonesia

[3]Department of Anatomy, Faculty of Medicine, Universitas Sumatera Utara Jl. Dr. Mansyur No.5 Medan 20155, Indonesia

Article Info: Received 18 March 2020; Accepted 25 April 2020
DOI: https://doi.org/10.32553/ijmbs.v4i4.1094
Corresponding author: S Mulyani
Conflict of interest: No conflict of interest.

Abstracts

Monosodium glutamate (MSG) is a food additive used in processed food. Long time use of MSG causes oxidative stress and damages kidney. The lycopene content in watermelon is potential in reducing oxidative stress. This research aimed to discover the effect of watermelon juice in preventing kidney damage in rats.30 Wistar rats were divided into 5 groups: four groups fed with 10 mg of MSG / g body weight; three groups of these also fed with 3 different concentrations of watermelon juice (25% in P1, 50% in P2, and 100% in P3) whereas the MSG only is as the control positive (KP). The fifth group is supplemented with water as the negative control (KN).Blood and kidney were taken after 30 days experiment. The urea levels were significantly higher in P1 (p=0.00) and P3 (p=0.01) in compare to KN, by 67% and 54% respectively. Creatinine levels were significantly lower in all watermelon intake groups by 32-46% in compare to KP. Kidney damages were obvious in group KP (p=0.00) and P1 (p=0.01). This research demonstrated that MSG exposure caused kidney damages and decreased kidney function. Watermelon juice at the concentration of 50% is able to reduce kidney damages by 48%.

Keywords: monosodium glutamate, kidney, watermelon juice, wistarrats

Introduction

Monosodium Glutamate (MSG) is sodium salts made of glutamate acid in form of purified hydrolyzed protein[1]. MSGis used as food additives (flavoring ingredients), by producing savory or delicious taste or more known as umami taste [2]. MSG is often found in processed foods such as sausages, mayonnaise, tomato sauce, canned vegetables, soup, flavors of chicken nuggets, hamburgers, fried chicken and seasoning used in french-fries, flavorful snacks such as chips, instant noodles, and seasoned salt[3, 4]. However, manufacturers do not always mention how much MSG is used in the packaging labels [5].

The data from Riskesdas (Basic Health Researches) in 2013 illustrated that flavoring ingredientsare classified into the high-risk food group that is widely consumed by Indonesian people (77.3%),surpassed the risk of other food groups such as sweet food (53.1 %) and fatty food (40.7 %)[6].

MSG has toxic effects and can cause damages on organs such as liver, kidney, heart, brain, reproductive organs, adrenal glands and fetal growth. Thereby increasing the risk of hypertension, obesity, stroke, and other health problems. The effects of MSG consumption can cause some symptoms such as numbness/tingling, fatigue, dizziness, and headaches. MSG is also assumed to play a role in triggering asthma, urticarial, atopic dermatitis, ventricular arrhythmias, neuropathic and stomach discomfort [7, 8, 9].

However, the effect of MSG consumption on health is still on a debate. The Food and Drug Administration (FDA) generally states that the safe limit of MSG consumption is not to exceed 3 grams per time, with the safe consumption limit not exceeding 120 mg/kg of body weight/day. The average consumption in Indonesian society is 0.6 g/day. In Japan and Korea, the daily MSG intake averages 1.2-1.7 g/day. But the fact is that the MSG is unconsciously consumed up to 10 g/day because the level of MSG in processed food is not listed in its packaging labels[10, 11].

The toxic levels of MSG in experimental animals were found in doses between 3 to 6 mg/g BW for 45 days. Histological changes were found in glomerulus in the form of infiltrates with vacuolization, pyknotic, Bowman's space dilatation, degeneration of the tubular epithelial layers, and decreased of kidney function indicated by declining serum urea and creatinine levels [12, 13].

Kidney damage and decreased function due to MSG cause an increase in reactive oxygen species (ROS) that result in oxidative stress. MSG causes an increase in succinyl CoA ligase that increases α-ketoglutarate dehydrogenase (α - KGDH) activity and ROS production. An increase in α-ketoglutarate also occurs as MSG increases glyceraldehyde 3 phosphate dehydrogenases which causes catalysis of NADH-dependent superoxide. MSG increases intracellular Ca^{2+} via (N-methyl-D-aspartate)NMDA that activates nitrate synthase and protein kinase C. The activation of nitric oxide synthase and protein kinase C activates free radicals and lipid peroxidation that play a role in oxidative stress [14].

The increase in oxidative stress can be reduced by consuming fruits or vegetables that are rich in antioxidants. One compound in fruits and vegetables that functions as an antioxidant is lycopene. Lycopene is a phytochemical hydrocarbon of the carotenoid group which acts as an antioxidant and is conjugated in counteracting the lipid peroxidation radicals[15]. Lycopene is found in some fruits such as watermelons which contain 4.5 mg/100 g of fresh weight [16].

Watermelons (*Citrulluslanatus)* areone of widely preferred fruitsfor its taste and water content [17]. It is well known that watermelons are effective to reduce oxidative stress by phytochemical lycopene[18].

1. Methods

This is an experimental study with the post-test only control group design. The rats were fostered at the Department of Pharmacology.Histological preparation of samples and analysis of histopathological changes conducted at the Anatomical Pathology Laboratory. Serum creatinine and urea levelswere analyzed at the Integrated Laboratory of the Faculty of Medicine. The research used 30 male Wistar rats (*RattusNovergicus*), 8 – 12weeks old and body weight 150 - 200 g. The rats were divided into 5 groups, consisting of 3 treatment groups (P1, P2, and P3), 1 positive control group (KP) and 1 negative control group (KN), 6 rats each. Drop Out criteria were 1) rats become sick during the keeping period (observation period, 7 days before treatment); 2) sick or died during treatment; 3) sick or died before terminated for sampling.

1.1 Procedure

This research was approved by the Animal Research Ethics Committee of the Faculty of Mathematics and Natural Sciences/AREC FMIPA of University of Sumatera Utara (Registration number 0411/KEPH-FMIPA/2019. Before conducting the research, the rats were raised for one week, at natural temperatures and equipped with food and water. They were divided into 5 groups consisting of: negative control group (KN), positive control group (KP) given 10 mg/g BW of MSG, Treatment Group 1(P1) given 10 mg/g BW of MSG plus 25% concentration of watermelon juice, treatment group 2(P2) given 10 mg/g BW of MSG and 50% concentration of watermelon juice, treatment group 3(P3) given 10 mg/g BW of MSG plus 10% concentration of watermelon juice, orally for 30 days.

Watermelon Juice Making. Watermelons were washed cleanly to remove dirt and insecticide residues, cut the red to white part, and weighed 15 kg to produce ± 13 L of watermelon juice (containing ±681.72 mg lycopene), by blending with a blender for 2 minutes (during the blending process, the blender is switched on intermittently to reduce heating to the blender). Then, the blended watermelons were filtered using a filter to separate the juice from the pulp. After that, the watermelon juice was stored in a freezer at temperature of -20° C in separate packages (each containing 450 ml, for daily administration). On the day of administration, the juice was firstly from the freezer ± 2 hours before administration. The dilution was done by pouring the juice into 2 cups of 20 ml each. The first glass as dose I had 100% concentration, the second glass was added with 20 ml of water as dose II had 50% concentration, and then 20 ml of the second glass was added with 20 ml of water as dose III with 25% concentration.

*Supplementation of MSG and Watermelon Juice.*MSG (10 mg/g BW) was givenorally, watermelon juice was given by *ad libitum* feeding.

Sampling. Rats were *sacrificed* on the 31st day, after weighing. Surgeries were performed, then blood samples were taken with *cardiac puncture.*The blood was put into a *vacutainer* tube and centrifuged 6000 rpm for 15 minutes. Serum samples obtained were transferred to a 1.5 ml micro tube and stored at -20°C for further assay. Then, the kidney samples were taken and cleaned using 0.9% of NaCl.

Preparations and Histological Examination. Organ samples were put into 10% of formalin buffer. Then dehydration was done through a series of alcohol solutions, and impregnation was done next (paraffin infiltration) using liquid paraffin, and next was *Embedding* (paraffinization), *sectioning* (pemotongan), using a 5µm microtome, *staining*using *Hematoxylin Eosin* (H&E) and examining under a light microscope (*Olympus CX21,*with magnification of 40x and 400x).

Observations were made by dividing the preparations into 4 parts, the percentage of kidney damage area from the four parts was added up and divided by four. The extent of cellular damage to the glomerulus was indicated by hyper cellularity (caused byinfiltration and proliferation of endothelial and mesangial cells*), atrophy* (indicated by *Bowman*'s dilatation and glomerular contraction, proximal tubules and distal tubules), and necrosis(indicated bydegeneration of nucleus such as karyopyknotic, karyorrhexis, and karyolitic).

Assessment of the kidney damage level is made according to Santoso et al.(2006) as follows: Score 1 (Normal) if kidney damage is not found; Score 2 (Mild) if kidney damage area is < 25%;Score 3 (Moderate) if kidney damage area is 25-50%; andScore 4 (Severe) if kidney damage area is> 50%

*Urea Level Assessment.*Serum urea levels were examined using Urea kit (Glory Diagnostic and random). Urea mono-reagent was made by mixing reagent 1 and 2 with scale 1 : 2. Mono-reagent was left for 30 minutes. It must not be exposed to light. After the mono-reagent was stable,1000 µl of mono-reagent was mixed with 10 µl of serum samples, serum urea levels were assessed using a UV spectrophotometer in the first and second minutes. Then the absorbance assessment results were input into the urea calculation formula, as follows:

$$\text{Urea} = \frac{\Delta A \text{ Samples} \times \text{standard concentration (mg/dL)}}{\Delta A \text{ Standard}}$$

Notes:
ΔA Samples = A1-A2
Standard Concentration = 50 mg/dl

*Serum Creatinine Levels Assessment.*Serum creatinine levels were assessed by creatininekit (Glory Diagnostic and random). Creatinine mono-reagent was made by mixing reagent 1 and 2 with scale 4:1. Then, 1000 µl of mono-reagent was mixed with 50 µl serum samples; serum creatinine was assessed using a visible spectrophotometer in the first and third minutes. then the absorbance assessment results were input into the creatinine calculation formula, as follows:

$$\text{Urea} = \frac{\Delta A \text{ Samples} \times \text{standard concentration (mg/dL)}}{\Delta A \text{ Standard}}$$

Notes :
ΔA Samples = A2-A1
Standard Concentration = 2 mg/dl

2.2 Data Analysis

The data among treatment groups were analyzed by using ANOVA testing. If a significant change is found, it is proceeded to Post Hoc testing with LSD analysis at rate of 5%, and tested by Mann Whitney testing to compare the results among the groups.

2. Results and Discussions

The research on the influence of watermelon juice on rats' kidneys which were exposed to MSG discovered rats' kidney functions andhistopathological description.

2.1 Kidney Function

Table 1 shows that the highest mean of serum urea is found in group P1 (8.02±2.26 µmol/l) whereas the highest mean of serum creatinine is found in group KP (63.97±12.63 µmol/l). The results of the statistical test found out that urea levels were found higher and different in groups KP (p=0.01), P1 (p=0.00) and P3 (p=0.02) compared to group KN. Creatinine levels were found lower and significantly different from control groups in groups P1 (p=0.00), P2 (p=0.04) and P3 (p =0.02).

Table 1: Urea and Creatinine Levels

Group	Serum Urea (µmol/l)	Serum Creatinine (µmol/l)
KN	4.81± 0.68	59.43±6.05
KP	7.56± 2.05*	63.97±12.63
P1	8.02± 2.26*	34.33±11.75*
P2	5.58± 1.68	43.21±6.29*
P3	7.41±1.52*	42.02±4.66*

Values: Mean ± SD. Negative control (KN), Positive control (KP); Treatments (P1, P2, P3). N=6. *Significant difference compared to positive control group(KP).

2.2 Kidney Hispathology

Table 2 demonstrates that the normal kidney structure are mostly found in group KN (66.67%), the mild damages were mostly found in groups P1 and P3 (66.67%), the moderate damages were mostly found in group KP (50%) and the severe damages were mostly found in group KP (50%). The statistical testing results showed that the kidney damage scores were higher and significantly different in KP (p=0.00) and P1 (p=0.08) compared to KN.

Table 2: The structural damage scores of rats' kidneys

Group	Kidney damage level in number and percentage				TOTAL	Mean of Kidney Damage
	(1) Normal	(2) Mild	(3) moderate	(4) (Severe)		
KN	66.67	33.33	0	0	100	1.33±0.52
KP	0	0	50	50	100	3.50±0.55*
P1	0	66.67	33.33	0	100	2.33±0.52*
P2	33.33	50.00	16.67	0	100	1.83±0.75
P3	16.67	66.67	16.67	0	100	2.00±0.63

Values:Mean ± SD. N=6 . Negative control (KN); Positive control (KP); Treatment (P1, P2, P3). N=6. *Significantly different from KN

Table 3 shows that the highest mean of Bowman's capsule diameter is found in group P2 (60.59±6.70 µm) while the lowest one is found in group KP (55.07±5.84 µm), the largest diameter of glomerulus is found in group P2 (43.56±6.27 µm) and the smallest is found in group KP (38.78±5.50µm), the highest mean of the differences between Bowman's capsule diameter and glomerulus is found in group P3 (0.758 µm). The statistical testing results found out that the mean of glomerulus diameter in group P1 is smaller and significantly different (0.035) than that of in gourp KN.

Table 3: Bowman and glomerulus

Group	Diameter of Bowman Capsule (μm)	Diameter of glomerulus (μm)
KN	60.05±2.75	47.93±3.16
KP	55.07±5.84	39.55±5,35*
P1	55.08±7.41	36.94±4.21*
P2	60.59±6.70	45.23±7.08
P3	59.01±4.49	43.65±5.04

Mean ± SD. N=6 Negative control (KN); N=6Positive control (KP); N=6 Treatment (P1,P2,P3). * Significantly different from KN

The research analysis found out that the administration of 10 mg/g of BW caused differences in serum creatinine statistically between the groups receiving 25% concentration of watermelon juice (p=0.00), 50% (p=0.04) and 100% (p=0.02) compared to the groups that were not given any watermelon juice. Previous researches also discovered significant differences between control groups and treatment groups. MSG consumed in high dose and for a long time can be toxic to kidneys [1].

The increase in urea and creatinine levels is one of the indicators to find out nephron functions and its damage caused by its activities [19]. MSG can disturb the metabolism of creatinine leading to an increase in muscle synthesis. Exposure to MSG can bring bad effect on kidney functions due to oxidative stress. The supplementation of watermelon juice to groups P1, P2 and P3 had positive effects on kidney functions in which the value of(p=0.013). This is because watermelons contain the source of bioavailable compound including lycopene and carotenoid functioning as antioxidants.

The assessment of histopathology found out that the kidney damage scores were higher and significantly different from the negative control group which was not exposed to MSG. This is in line with the previous research in which rats that were exposed to MSG had kidney damages [11, 20].

The supplementation of MSG in the positive control group (KP) caused damages in glomerulus such as vacuoles atrophy and Bowman capsule dilatation, proving that the administration of MSG in quite high dose for a long-time period could be toxic to kidneys. This is in line with the research done by Simon (2013) finding out that the longer the exposure to MSG is, the higher the number of cellular damages is. MSG can induce the changes in kidney cytoarchitecture, increase hyper cellular glomerulus, infiltrate the inflammatory cells in kidney cortex, edema of tubular cells, and finally degenerate kidney tubules. Kidneys that are exposed to MSG can cause the oxidative stress which brings bad effects on kidney function. According to [7], it decreases serum urea levels and increases serum creatinine levels. MSG can also damage kidney tissue by inducing oxidant stress that changes the description of kidney histopathology. The research done by Singh et al, 2014, states that kidney structure becomes not regular, glomerulus undergoes vacuoles partial atrophy, nucleus pyknotic and dilatation of Bowman capsule. The display of kidney tubules is indicated by epithelial layer degeneration [11].

Meanwhile, the research byElbassuaoni studying the effect of MSG on kidney function, discovered a description of photomicrographs, showing irregular kidney structure, glomerulus with vacuoles partial atrophy, nucleus pyknoticinti pyknotic and dilatation of Bowman capsule. The display of kidney tubules is indicated by epithelial layer degeneration, in line with the research done by Minarma, on description of kidney histology and function after administration of MSG; the results demonstrated changes in the description of kidney histopathology i.e. edema in glomerulus and kidney tubular cells.

Damages in either glomerulus or tubules caused by imbalanced reactive oxygen stress (ROS) are resulted from MSG. The activities of N-methyl-D-aspartate (NMDA) receptor, metabotropic glutamate receptor (mGluR) and cysteine-glutamate antiporter are excessive, so that the glutamate levels increases and amino acid is filtrated freely by glomerulus which is followed by an increase in calcium in cytoplasm leading to disorders in $Na^{-}K$ ATPase canal [13]

The study done by Pinto 2001, found out that consumption of 150 ml of watermelon juice could produce antioxidant effects in humans' blood [24]. Daily intake of 5 mg lycopene is effective to ve antioxidants compared to higher intake more than 20 until 30 mg per day, due to limited absorbance of lycopene [25]. According to Rao, the recommended daily intake of lycopene averages in 5-10 mg per day, in which watermelon can be consumed in form of juice or fresh fruit [26].Lycopene functioning as antioxidants is also conjugated in repelling lipid peroxidation radicals, reactive oxygen species (ROS), and nitrate oxide [27].

Some researches demonstrate that lycopene had positive influences on humans' health because of it various natures. It functions as antioxidant and has the most efficient capacity of oxygen single quenching and natural carotenoid (ten times more effective than α-tocopherol). In addition, it also protects biomolecules from oxidative damages, impedes cellular proliferation, and modulates communication intracellular, particularly in stimulating gap junctional communication (GJC) [17]. The mechanism of lycopene in preventing oxidative stress in MSC (Cytoplasmic Membrane) is that oxidative stress triggers induction of reactive oxygen species (ROS) in MSC. ROS leads to phosphorylation of ATM and the signaling path related to apoptosis (p38 and JNK), resulting in augmentation of p53 phosphorylation. Furthermore, ROS

breaks the balance between Bax and Bcl2, resulting in induction of apoptosis through division of PARP-1 and Caspase-3. Lycopene depresses apoptosis yang induced by oxidative stress through akt-MnSOD. Moreover, lycopene decreases phosphorylation of MAPK related to apoptosis (p38 and JNK). This effect of lycopene on oxidative stress induces a decrease in phosphorylation of ATM-p53 signaling path, and protection for PARP-1 and caspase-3 divisions, resulting in prevention of apoptosis and augmentation of life continuity in MSC. ATM; ataxia telangiectasia mutates serine / threonine protein kinase, MAPK; protein kinase is activated by mitogen, PARP-1; poly [ADP-ribose] polymerase 1, PI3K; phosphatidylinositol-4,5-bisphosphate 3-kinase [28].

3. Conclusion

The research results demonstrated that exposure to MSG can cause tissue damages and decreased kidney function. Watermelon juice 50% is able to repair oxidative stress which results in kidney damages.

Acknowledgments

The authors gratefully acknowledge that the present research is supported by University of Sumatera Utara.

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