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BENEFICIAL EFFECT OF VITAMIN-C ON MONOSODIUM GLUTAMATE INDUCED HEPATOTOXICITY IN RAT

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ABSTRACT

Present study has been undertaken to search the effect of vitamin-C on Mono Sodium Glutamate (MSG) induced hepatotoxicity in rat. MSG has impaired various parameters such as SGPT, SGOT, Alkaline phosphatase, total protein, serum SOD and catalase activity and the histological structure of liver significantly in all the experimental groups of animals. Significant improvement has also been noticed after applicatiuon of vitamin-C to the MSG treated animals of different doses along with improvement of histological status of liver.

KEYWORDS: Monosodium Glutamate, antioxidant, Alkaline phosphatase, histology, necrosis and hepatotoxicity.

INTRODUCTION

Various environmental chemicals, industrial pollutant and food additives have been implicated as causing harmful effects. Monosodium Glutamate (MSG) is one of the most widely used food-additives in commercial foods known as AJI-NOMOTO.[1] MSG is the sodium salt of glutamate and is simply glutamate, water and sodium. In the early 1900s scientists isolated the ingredient in plants that is the essential taste component responsible for greatly enhancing flavour.[2-7] In the early part of twentieth century, MSG was extracted from seaweed and other plant sources. Today, MSG is produced from many sugar cane or sugar beets, as well as starch and corn sugar. MSG when present in its free form, not bound together with other amino acids in protein, glutamate has a flavour enhancing effect in foods. When MSG is added to foods, it provides a flavouring function similar to naturally occurring free glutamate.[8] MSG is used to enhance the natural flavours of meats, poultry, sea foods, snacks and soups.[9]

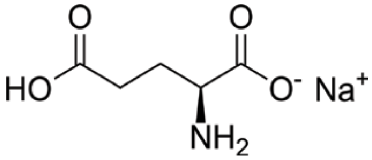


Figure 1: structure of MSG.

Its application has increased over time and it is found in many different ingredients and processed foods obtainable in every market or grocery store. MSG gives a special aroma to processed foods which is known as ‘umami’ in Japanese. This taste sensation is also called “savoury”.[10]

Beside its flavour enhancing effects, MSG has been associated with various forms of toxicity. MSG has been linked with obesity, metabolic disorders, Chinese restaurant syndrome, neurotoxin effects and detrimental effects on the reproductive organs. MSG acts on the glutamate receptors and releases neurotransmitters which play a vital role in normal physiological as well as pathological processes.[11] Glutamate receptors have three groups of metabotropic receptors (mGluR) and four classes of ionotropic receptors (NMDA, AMPA, delta and kainite receptors). All of these receptor types are present across the central nervous system. They are especially numerous in the hypothalamus, hippocampus and amygdala, where they control autonomic and metabolic activities.[12-13] Results from both animal and human studies have demonstrated that administration of even the lowest dose of MSG has toxic effects. Although MSG has proven its value as an enhancer of flavour, different studies have hinted at possible toxic effects related to this popular food-additive. These toxic effects include CNS disorder, obesity, disruptions in adipose tissue physiology, hepatic damage and reproductive malfunctions. These threats might have hitherto been underestimated. In the meantime, people keep using ever larger amounts of MSG unaware of the possible consequences. Further studies need to be undertaken in order to assess the connection between MSG and cardiovascular disorders, headache, and hypertension in human models. MSG is a controversial food-additive used in canned food, crackers, meat, salad dressings, frozen dinners and other products.

Vitamins have indispensable role in almost all biochemical reactions and they are ideal antioxidants able to increase tissue protection from oxidative stress due to their easy, effective and safe dietary administration in a large range of concentrations.[12,14]

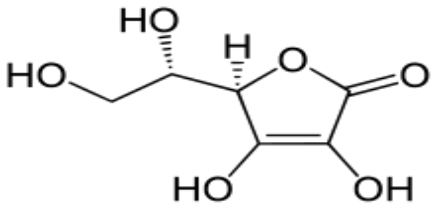


Figure 2: Structure of Vit-C.

L-ascorbic acid known as vitamin C, is the first to become depleted on the exposure to oxidative stress.[15] Normal L-ascorbate level has a therapeutic benefit due to its ability to reduce the oxidative stress by reacting with superoxide and hydroxide radicals as well as alkyl, peroxyl and alkoxyl radicals, thereby it can neutralize these radicals and stop the initiation and propagation of chain reaction.[16]

So, the present study has been undertaken to evaluate the damaging effect of MSG specifically on liver and also the protective effect of vitamin-C.

MATERIALS AND METHODS

Experimental Animals

Adult male rats weighing **120-130 g** were used in the present study. Rats are kept in well designed and cleaned polypropylene cages. They were maintained under Normal conditions and fed a normal diet with free access to Water ad libitum.

Animal grouping and treatment

Rats were randomly divided into **5 groups** having **6 rats in each group.**

Group I: This group of animals having healthy normal rats and serves as untreated control group. This group was given distilled water at a dose of **0.5 ml /100 gm** of body weight for 28 days.

Groups II-III: Animals of these groups were orally given Monosodium Glutamate at a dose of **1.5 gm/kg** and **4 gm/kg** body weight respectively for 28 days.

Groups IV-V: animals of these groups were orally given Monosodium Glutamate at a dose of **1.5 and 4 gm/kg** body weight in addition with vitamin C at a dose of 1.5 **gm/kg** body weight daily for 28 days.

At the end of the treatment, overnight fasted animals were sacrificed using diethyl ether, followed by cervical dislocation.

Animal sacrifice and measurement of parameters

At the end of the experimental duration of 28 days, the animals were weighed, anesthetized, and sacrificed.

The final body weights of all the rats were taken by the electronic balance. The rats were then anesthetized one after another with anesthetic ether followed by cervical dislocation and blood was collected directly from the hepatic portal vein and allowed to coagulate. Clear serum was collected and stored at 20°C for enzyme assay. Liver of each rat was dissected out and weights were taken with the help of electronic balance. Liver from each experimental animal was processed for histology and 5µ thick sections were taken and stained with hematoxylin and eosin[17] for further observation. Serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), and serum alkaline phosphatase (ALP) were measured of all the control and experimental animals by the supplied standard kit ("COGENT," Clinical Chemistry division of Span Diagnostics Ltd.). The total serum protein was estimated by the Lowry method with a standard curve of BSA.[18] Serum SOD and catalase activity were measured to determine the oxidative stress in all the experimental animals, including the control animals by the methods of Marklund and Marklund,[19] and Beers Jr. and Sizer[20] respectively.

Statistical Analysis

The statistical analysis was carried out by Student's "*t*" test[21] to generalize the results of various biochemical parameters of experimental groups in comparison to their respective control group and $P < 0.05$ was considered as a significant result.

RESULTS

Effect on Body Weight

The initial and final body weights of all rats in both control and treatment animals were presented in Table 1. There was no significant reduction in the body weights of both the low and high dose Monosodium Glutamate (MSG) treated groups (groups II-III), when compared to control group. After 28 days Treatment of the rats with Vitamin-C resulted normal growth pattern (groups IV and V).

Table 1: Results of body weight gain % of different experimental groups including the control group. Values are mean±SEM (gm, *n*=6) followed by two-tail *t*-test.

	Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
Initial	125.00±5.62	127.00±5.43	126.00±4.99	126.00±5.91	125.00±4.94
Final	136.00±5.91	134.00±4.92	137.00±5.71	135.00±6.01	139.00±5.21

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on liver weight

Weight of the liver of MSG induced rat was significantly ($p<0.05$) increased in comparison with control group of animals. It has been also reduced towards control significantly ($p<0.05$) after supplementation of vitamin C in respect of MSG treated groups of rat.

Table 2: Results of liver weight of different experimental groups including the control group. Values are mean±SEM (gm%, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
2.914±0.201	3.119±0.233	3.481±0.341	3.057±0.299	3.290±0.216

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on SGPT

SGPT level was increased significantly ($p<0.05$) after MSG administration in dose dependent manner when compared with control animals. After administration of vitamin C, it has been decreased towards normal range in significant way ($p<0.05$).

Table 3: Results of SGPT of different experimental groups including the control group. Values are mean±SEM (IU/L, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
32.10±3.62	48.62±3.41	54.28±3.63	40.14±3.23	46.64±3.69

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on SGOT

Levels of SGOT in MSG treated groups of animals were significantly ($p<0.05$) increased in dose dependent manner in comparison with the control animal. Supplementation of vitamin C reduced this level significantly ($p<0.05$) when compared with MSG treated animals.

Table 4: Results of SGOT of different experimental groups including the control group. Values are mean±SEM (IU/L, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
45.60±4.21	62.03±4.03	72.32±4.23	49.52±3.91	61.10±4.83

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on Alkaline phosphatise

As the increased levels of SGPT and SGOT observed in MSG treated animals, Alkaline Phosphatase level was also increased in MSG treated animal in significant way ($p<0.05$). Also the reduction in Alkaline phosphatase level was observed after supplementation of vitamin C in significant manner ($p<0.05$) in both the treated groups.

Table 5: Results of Alkaline phosphatase of different experimental groups including the control group. Values are mean±SEM (IU/L *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
68.18±3.93	89.65±4.41	110.02±5.02	78.22±4.85	97.32±4.74

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on Total protein

Level of total protein has been significantly ($p<0.05$) reduced in MSG treated animals in comparison with the control group of animals. Supplementation of vitamin C has increased the total protein level towards normal range in significant manner ($p<0.05$) when compared with MSG treated group of animals.

Table 6: Results of serum total protein of different experimental groups including the control group. Values are mean±SEM (gm/100ml, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
6.82±0.69	6.10±0.47	5.86±0.57	6.40±0.91	6.20±0.83

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on SOD activity

SOD activity was decreased significantly after application of MSG in dose dependent manner in comparison with the control group of animals. Supplementation of vitamin C has shown marked increase in SOD activity in both the experimental groups of animals.

Table 7: Results of serum SOD activity of different experimental groups including the control group. Values are mean±SEM (U/ml, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
60.82±1.29	39.10±1.47	36.86±1.57	56.40±1.71	52.20±1.53

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Effect on catalase activity

Catalase activity has been significantly decreased after MSG application in both the experimental groups in comparison to the control group. Significant rise in this parameter has also been noticed after vitamin C supplementation in dose dependent manner.

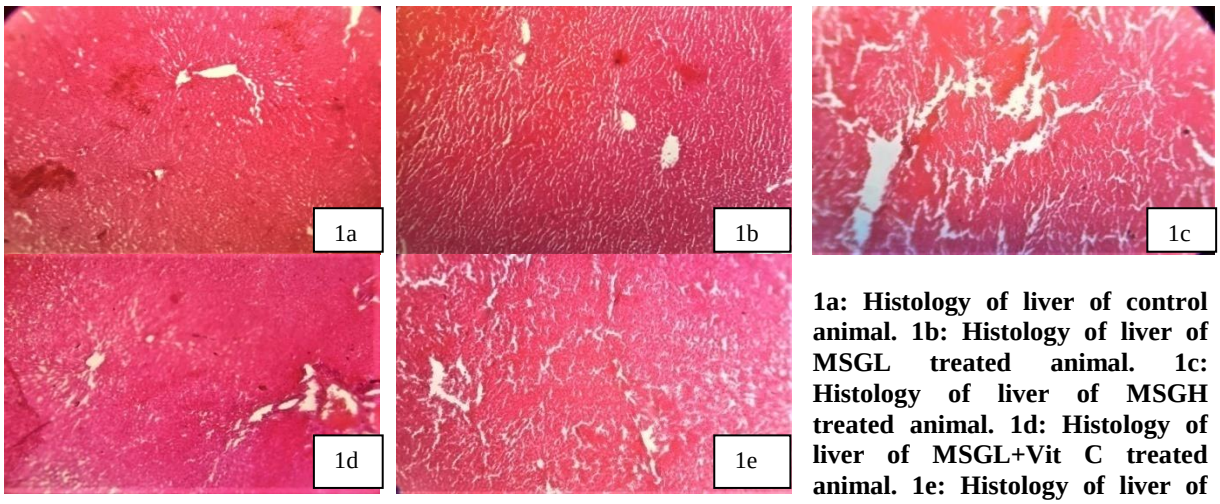
Table 8: Results of serum catalase activity of different experimental groups including the control group. Values are mean±SEM (U/ml, *n*=6) followed by two-tail *t*-test.

Gr-I(Control)	Gr-II(MSGL)	Gr-III(MSGH)	Gr-IV(MSGL+Vit C)	Gr-V(MSGH+Vit C)
48.32±1.67	36.34±1.39	31.56±1.45	41.63±1.47	39.94±1.39

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

Histopathological effect

After administration of MSG, the structure of liver has been changed significantly. The structural change observed after the application of the drug was in dose dependent manner. The improvement was also seen after vitamin C supplementation in both the MSG applied groups of experimental animals.



1a: Histology of liver of control animal. 1b: Histology of liver of MSGL treated animal. 1c: Histology of liver of MSGH treated animal. 1d: Histology of liver of MSGL+Vit C treated animal. 1e: Histology of liver of MSGH+Vit C treated animal.

Figure: 1(a-e): Histological structure of liver of control, MSG treated and Vitamin C supplemented animals.

**** MSGL-Monosodium Glutarate low dose group, MSGH-Monosodium Glutarate high dose group, MSGL+Vit C- Monosodium Glutarate low dose with vitamin C, MSGH+Vit C- Monosodium Glutarate high dose with Vit C.**

DISCUSSION

The present observation leads to disclose the effect of vitamin C on MSG induced liver of experimental rats. It has been well observed that, application of MSG has shown no significant effect on general growth i.e. body weight of experimental rats of two groups. So, obviously, there was no such difference found regarding the body weight changes among all the experimental groups of

animals. As the MSG intake proportionately increases the energy intake, it might be the probable cause of insignificant changes of general growth of experimental rats of MSG treated groups.[22-24]

After application of MSG, significant increment in liver weight has been found in experimental rats in dose dependent manner like earlier studies[25-26] (Fig.1A). This weight increment may have its reflection on liver inflammation.[27] Supplementation of vitamin C has balanced the weight of liver in experimental animals significantly. It might be due to antioxidant activity of vitamin C.[28] Oxidative stress which was shown in MSG treated animals has been taken off after supplementation of antioxidant agent like vitamin C. This observation is well supported by earlier study.[29]

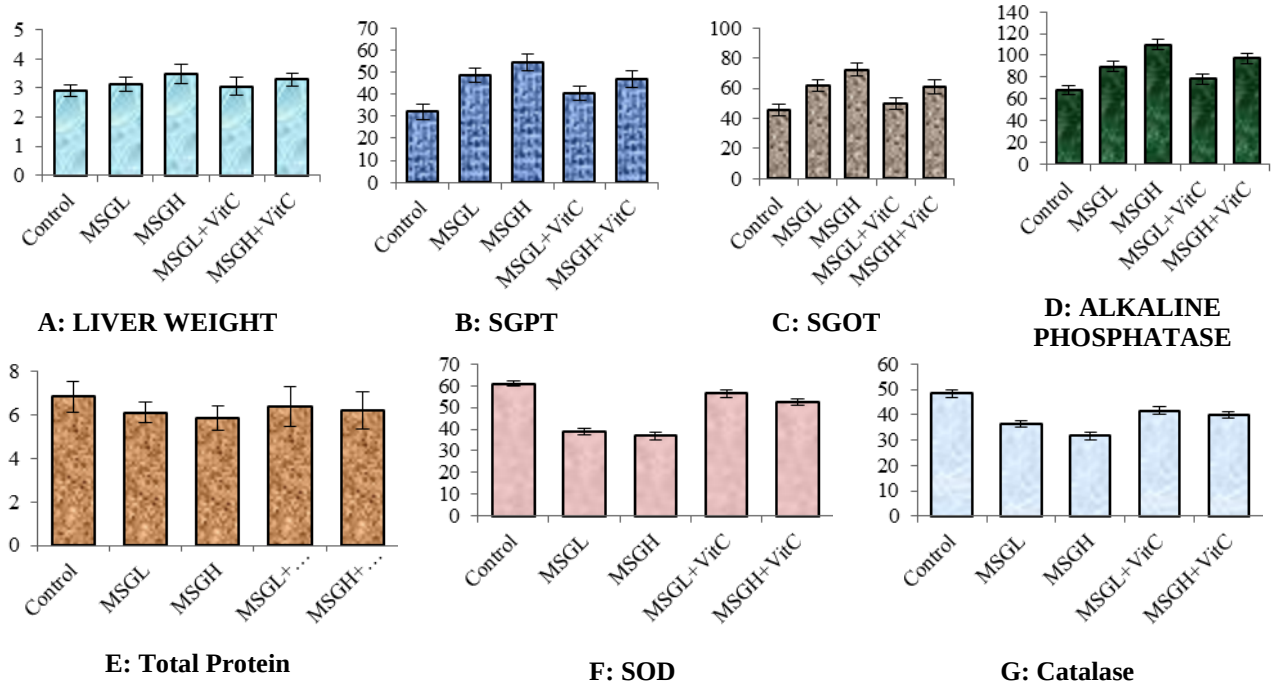


Fig. 1(A-G): Graphical presentation of different parameters involving control, MSG treated and vitamin C treated animals.

SGPT is thought to be concerned with the integrity of the mitochondria[30] and it is also abundant in liver and acts as a marker of metabolic activity.[31] In the present study, significant increase in SGPT level was found in all the MSG treated animals in dose dependent manner. Supplementation of vitamin C has shown its effect to reduce back the level of SGPT towards its normal value significantly in both the experimental groups (Fig.1B). So, there may be the metabolic disruption after administration of MSG. SGOT has integrity with lysosomes[32] and adrenal corticoids stimulate SGOT activity[33] (Fig.1C). SGOT and Alkaline phosphatise has shown same type of effect after administration of MSG dose dependently (Fig.1D). Significant balance was also found after supplementation with vitamin C in case of both these parameters like SGPT.

All the metabolic marker enzymes have been disturbed after administration of MSG in experimental animals in this present study. SOD was significantly decreased in experimental animals in dose dependent manner (Fig.1F). So, superoxide might be produced as a by-product of oxygen metabolism which is harmful agent may cause many types of cell damage.[34] Catalase activity was also decreased in both the experimental groups indicating the oxidative stress (Fig.1G). Catalase catalyzes the decomposition of hydrogen peroxide to water and oxygen[35] and serves as an important enzyme in protecting the cell from oxidative damage by reactive oxygen species. Present study indicates significant reduction in catalase activity in both the MSG treated experimental groups in dose dependent manner. After vitamin C supplementation, the activity of the same enzyme has been recovered significantly.

After application of MSG, total serum protein was significantly reduced in both the experimental groups which were recovered well after vitamin C supplementation (Fig.1E). This might be due to increased oxidative stress after MSG application. Oxidative stress may cause free radical formation which leads oxidative damage in many molecules, such as lipids, proteins and nucleic acids. Many diseases have criticality been attributed to oxidative damage including atherosclerosis, aging, and cancerous diseases. Antioxidant foods are protective agents against these ailments.[36]

Consistent lesions that included Cytoplasmic fatty vacuolation of centrilobular hepatocytes have been found after MSG treatment in both the experimental animal

groups. Isolated cell necrosis is also prominent in these two MSG treated group. Vitamin C supplementation has improved these histopathological conditions in present study.

CONCLUSION

In this context, it can be said that, MSG application has hampered the activities of major enzymes of liver in both the experimental animal groups. It also altered the histopathological status of liver. The oxidative stress is also prominent in both the treated groups indicating the loss of activity of SOD and Catalase. Supplementation with Vitamin C has improved all these negative effects of MSG due to its antioxidant properties.

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