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Neuroprotective Effect of Bee Venom and Proplis Against Monosodium Glutamate Induced Brain Toxicity in Rats

Alyae, M.S. Gabal

Biochemistry and Nutrition Department, Women's College, Ain Shams University, Cairo, Egypt.

Abstract

This study aimed to investigate the neuroprotective effect of bee products as bee venom and proplis ethanolic extract (PEE) against brain toxicity induced by food additive monosodium glutamate (MSG) on brain neurotransmitters and oxidative status in adult male albino rats.40 adult albino rats of Sprague-Dawely strains weighing (140±40) g were divided into four groups of ten animals each as follow: **Group I:** healthy control; **Group II:** MSG control received (300mg of MSG in distilled water /kg/day/orally) ,**Group III** and **IV** : rats received (300mg of MSG in distilled water/kg/day/orally) and supplemented with bee venom or PEE (1 mg /kg /day intraperitoneally) for 21 days respectively. Results showed a massive increase in brain neurotransmitters and oxidative biomarkers levels with a compatibility decrease in acetylcholine esterase (AchE) as well as antioxidants activities in the MSG control group. The groups of rats supplemented with bee venom or PEE exerted a beneficial effect on all parameters. Whereas, the rats administered bee venom had the significantly highest improvement of all the estimated parameters ($P \leq 0.05$) compared with the MSG control group. The bee products like bee venom and PEE could trigger the MSG brain damage induced in rats.

Keywords: monosodium glutamate, bee venom, proplis ethanolic extract, brain neurotransmitters, brain oxidative status

1. Introduction

Monosodium glutamate (MSG, $C_5H_8NO_4Na$), the sodium salt of glutamic acid. It is found naturally in many protein-rich food items as well as some vegetables . MSG is used as a flavor enhancer (E621) and food-additives in commercial foods to increase food palatability and intake. In many countries MSG goes by the name "China salt". Although, its flavour enhancing effects, MSG has been associated with different forms of toxicity in humans and laboratory animals especially at high doses ***(Niaz et al., 2018)***.

MSG is a natural brain neurotransmitter, a substrate for glutathione synthesis as well as an energy source for certain tissues. Free glutamic acid can cause problems because of its many receptors in brain tissues. Hypothalamus also, do not have an impermeable blood–brain barrier. Thus, free glutamic acid from food sources can get into the brain, injuring and causing many allergic reactions. High daily intake of MSG results in accumulation and consequently rise of glutamic acid in the blood, long-term intake of MSG was shown to induce many tissues impairments (***Hussein et al., 2017***).

The practice of using bee products like (raw honey, propolis, bee venom, royal jelly as well as pollen) for medical conditions is known as apitherapy . Bee products are found to be a potential source of natural antioxidants as phenolic acids and flavonoids. (***Kocot et al., 2018***).

Attention has been given to the venom of some animals in development of new treatments for several diseases. Bee venom (BV) is a bitter colorless liquid (pH 4.5–5.5) that is soluble in water but insoluble in alcohol. A bee can inject up to 0.1mg venom via its stinger. The venom is mainly produced in the abdomen of the bees and originates from a mixture of acidic and basic secretions ***(Hossen et al., 2017)***. BV is a complex mixture of peptides, non-peptides, enzymes, some sugars and low molecular components. BV has therapeutic effects against several diseases (***Elkotby et al., 2018***).

Propolis (bee glue) is the resinous substance collected by bees from the leaf barks and buds of trees. It appears to have antibacterial, anti-inflammatory, antioxidant , and immune-stimulating activity. Propolis have high flavonoid contents as aldehydes, caffeic acid, and caffeic acid phenethyl ester (***Hussein et al., 2017***)

2. Materials and Methods

2.1 Chemicals

Monosodium glutamate (MSG) was the purest grades available Sigma Aldrich (USA), Bee venom (BV) Lypholized *Apis mellifera* purified bee venom (VACSERA, Egypt, 1mg/ vial) was used and Proplis, the yellow-brown propolis sample produced by *Apis mellifera* bees was purchased from Agricultural Research Centre (ARE) and extracted in ethanol forming proplis ethanolic extract (PEE) according to ***(Da Silveira et al., 2016)*** method.

All chemicals and reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA), and EL-Gomhouria Company for Trading Chemicals (Cairo, Egypt).

Dopamine (DO), serotonin (SE) acetylcholine esterase (AchE), and glutamate (GLU) assay Eliza kits were purchased from MyBioSource, (San Diego, CA, USA). DNA oxidative marker 8-hydroxydeoxyguanosine (8-OHdG) assay and protein carbonyl group Eliza kits were purchased from *Cell Biolabs* (San Diego, CA , USA). Other kits were purchased from Biodiagnostics (Giza, Egypt).

2.2. Experimental animals and design: 40 Adult male albino rats "Sprague-Dawely strain" weighing (140±40) g were supplied from the Animal House of Research Institute of Ophthalmology, Giza, Egypt. Rats were acclimatized to laboratory conditions for 3 days, maintained at constant 24 °C with 12 h light-dark cycle and fed with balanced rodent pellet diet and water *ad libitum*. After acclimatization, the rats were randomized into four experimental groups (n = 10); divided as follow **Group (1)** Healthy control , rats were given distilled water daily orally and injected with normal saline intraperitoneally (i.p.) for 3 weeks, **Group (2):** MSG control group, rats received (300mg of MSG in distilled water /kg/day/orally) and injected with normal saline interperitonially (i.p) for 3 weeks ***(Zanfirescu et al., 2017)***, **Group (3):** Bee venom group, rats received (300mg of MSG in distilled water /kg/day/orally) and injected with (1 mg bee venom (BV) /kg /day i.p) for 3 weeks ***(Dantas et al., 2014)***, **Group (4):** Proplis group, rats received (300mg of MSG in distilled water /kg/day/orally) and injected with (1 mg proplis ethanolic extract (PEE) /kg /day i.p) for 3 weeks ***(Da Silveira et al., 2016)***.

2.3. Sample collection: At the end of the experimental duration (3 weeks), rats were sacrificed under ether anesthesia after an overnight fasting. The brain samples were immediately removed and washed with ice-cold phosphate buffered saline and the cerebellum region was dissected as the method given by ***Glowinski and Iverson (1996)***. The homogenate (10% w/v) was rinsed with saline (0.9% NaCl), dried, and homogenized in a phosphate buffer (10 mM, pH 7.4) that contained 1.15% potassium chloride and 1.15% ethylene-diamine tetra-acetic acid (EDTA), and centrifuged at 3000 rpm for 15 min to obtain tissue lysates. The tissue lysates were collected and kept at −20 °C to be used for the estimation of different parameters, as described below (***Ashok et al., 2013***).

2.4. Biochemical determinations: The values of neurotransmitters; DO, SE , GLU as well as AchE activity were determined in brain homogenate according to the methods of (***Kim et al., 2008; Torfs et al., 2012, De la Mora, 1989*** and ***Ellman et al., 1961***) respectively . Antioxidants determination like super oxide dismutase (SOD), catalase (CAT) activities and Glutathione level in brain homogenate according to *(**Nishikimi et al., 1972**, **Aebi**, **1984** and **Beutler et al., 1963)* .The level of lipid peroxidation biomarker in brain homogenate malondialdehyde (MDA)was determined as described in the method of ***Draper and Hadley, (1990)***. The brain nitric oxide (NO), 8-OHdG and protein carbonyl group were determined according to (***Montgomery et al., 1961 , Patel et al., 2007 and Reznick and Packer, 1994)***.

2.5. Statistical analysis:

Results were analyzed using the SPSS software (version 16). (ANOVA; F-test) and least significant difference (L.S.D) were calculated according to ***Levesque (2007*)**.

3. Results

3.1. Effect of Bee venom and Proplis on AchE Activity as well as DO, SE and GLU Levels in MSG Intoxicated Rats

Table (1) displayed that the AchE activity decreased while levels of neurotransmitters DO, SE, and GLU were increased significantly in rats administered with MSG as compared to healthy control rats. While treatment with bee venom and proplis caused a significant improvement in these values.

Table (1) Effect of Bee venom and Proplis on AchE Activity as well as DO, SE and GLU Levels in MSG Intoxicated Rats

Groups / Parameters	AchE (µg/mg)	DO (µg/mg)	SE (ng/mg)	GLU (µg/mg)
Healthy control rats	18.19±0.39^{a}	0.66±0.051^{d}	156.75±3.30^{d}	5.95±0.13^{d}
MSG control rats	10.23±0.55^{d}	1.96±0.104^{a}	245.98±5.77^{a}	15.35±0.39^{a}
MSG intoxicated rats supplemented with bee venom	15.65±0.42^{b}	0.92±0.041^{c}	187.25±1.95^{c}	9.63±0.21^{c}
MSG intoxicated rats supplemented with proplis	13.7±0.18^{c}	1.29±0.022^{b}	207.45±2.21^{b}	12.77±0.62^{b}
L.S.D ($p \leq 0.05$)	1.091	0.193	9.757	0.788

Values are expressed as means ±S.D, n=10.
There was no significant difference between means have the same alphabetical superscripts letter in the same column. ($p \leq 0.05$).

3.2 . The Brain Oxidative Stress Markers of MSG Intoxicated Rats Administered with Bee venom and Proplis

Table (2) illustrated that MSG acts as a potent oxidant which caused a state of oxidative stress manifested by a massive increase in DNA oxidation product 8-OHdG and also in oxidative stress biomarkers like PCG , MDA and NO levels in MSG control rats as compared to healthy control rats. On the other hand administration of bee venom or proplis caused a significant decrease in oxidative stress makers as well as DNA oxidation product in treated groups in comparison with MSG control group .

Table (2)The Brain Oxidative Stress Markers of MSG Intoxicated Rats Administered with Bee venom and Proplis

Groups / Parameters	8-OHdG (ng/mg)	PCG (nmol/mg)	MDA (µmol/g)	NO (µmol/g)
Healthy control rats	0.813±0.03^{d}	5.32±0.25^{d}	1.06±0.11^{d}	3.8±0.32^{d}
MSG control rats	9.025±0.69^{a}	20.16±0.53^{a}	10.2±0.41^{a}	17.93±0.87^{a}
MSG intoxicated rats supplemented with bee venom	4.225±0.478^{c}	9.65±0.36^{c}	3.16±0.28^{c}	8.06±0.29^{c}
MSG intoxicated rats supplemented with proplis	7.052±0.258^{b}	12.8±0.46^{b}	5.41±0.18^{b}	11.9±0.63^{b}
L.S.D ($p \leq 0.05$)	1.367	1.072	0.656	0.879

Values are expressed as means ±S.D, n=10.
There was no significant difference between means have the same alphabetical superscripts letter in the same column. ($p \leq 0.05$).

3.3. Impact of Bee venom and Proplis Administration on Some Antioxidants in MSG Intoxicated Rats

Table (3): showed that MSG control group recorded the lowest CAT and SOD activities as well as GSH level as compared to healthy control group. While administration of bee venom and proplis improved these values. The most improvements were observed in bee venom treated group.

Table (3): Impact of Bee venom and Proplis Administration on Some Antioxidants in MSG Intoxicated Rats

Groups / Parameters	GSH (mg/g)	CAT (U/g)	SOD (U/g)
Healthy control rats	7.93±0.86[a]	37.8±0.42[a]	3.021±0.227[a]
MSG control rats	2.75±0.41[d]	17.73±0.33[d]	1.013±0.059[d]
MSG intoxicated rats supplemented with bee venom	5.82±0.11[b]	30.06±0.22[b]	2.27±0.38[b]
MSG intoxicated rats supplemented with proplis	3.92±0.24[c]	24.82±0.51[c]	1.7±0.182[c]
L.S.D ($p \leq 0.05$)	0.722	1.129	0.557

Values are expressed as means ±S.D, n=10.
There was no significant difference between means have the same alphabetical superscripts letter in the same column. ($p \leq 0.05$).

4. Discussion

Food additives are substances which added during the processing or production of food. Monosodium Glutamate (MSG) is now used widely all over the world as a food additive to enhance flavor of the food products in addition to its use by house wives and chives during meals preparation. MSG occurs naturally at low concentrations bound to proteins in many plants and protein-rich food items. High concentrations of MSG as flavor-enhancing food additive is found in fast and commercially packaged food products such as soups ,chips, crackers, meats as well as many others (***Abu-Taweel, 2016***).

Consumption of MSG especially at high doses has been associated with various forms of toxicity. MSG has been linked with different diseases as obesity, metabolic disorders, Chinese Restaurant Syndrome, neuro-toxic 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 ***(Niaz et al., 2018).***

Studies revealed that consumption of MSG induce a state of oxidative stress which is believed to be behind most of the symptoms and health disorders that occur due to excessive use of this compound ***(Mahieu et al., 2016).*** Natural antioxidants protect against oxidative stress. Natural antioxidants have been reported to decrease free radical attack on bio-molecules and diminishing cumulative oxidative damage. The medicinal use of honey bee products (apitherapy) as natural antioxidants used since ancient times. It was producing a greatest number of biological effects used in experimental pharmacology ***(Salman et al., 2015).***

Bee venom, which is also known as apitoxin is a complex mixture of substances. It is used to defend the bee colony. Bee venom, is produced from the venom gland located in the abdominal cavity. It contains several biologically active peptides, including melittin, apamin, adolapin, mast cell degranulating peptide and many enzymes. Plus also non-peptide components, such as a variety of bioamines like apamin, histamine, procamine, serotonin, and nor-epinephrine, which facilitate nerve transmission and healing in a variety of nerve disorders. This gives bee venom the ability to travel along the neural pathways from the spine to various trigger points and injured areas to help repair nerve damage and restore mobility. Bee venom has traditionally been used as a non-steroidal anti-inflammatory drug for the relief of pain and the treatment of different diseases, such as rheumatoid arthritis and multiple sclerosis as well as in the treatment of tumors (***El-Bassiony et al., 2016***).

Propolis have a high content of antioxidants as polyphenols and flavonoids . Both substances have proven their ability to fight free radicals, on top of being able to protect lipids from being destroyed in the oxidative process. Propolis can be added to drinks, foods, chewing gum, cosmetics, and toothpaste. Propolis with highest antioxidant capacity has been linked to kaempferol and phenethyl esters, aldehydes, and caffeic acid ***(Zarate et al., 2018).***

The present study demonstrated that MSG administration caused some toxicological consequences in animal models. Also, potential properties of bee venom and propolis in restoring these toxicological consequences were investigated.

The brain is the most important organ of the central nervous system (CNS). It is more susceptible to damage by free radicals because of its high use of oxygen, its high content of polyunsaturated fatty acids such as archidonic acid and docosohexenoic acid, and its low concentration of antioxidant molecules compared to other tissues. In CNS, oxidative stress results in acute and chronic injury leading to the pathogenesis of neuronal damage .Free radicals attack unsaturated bonds of membrane fatty acids, leading to an autocatalytic process that can impair the function of membrane AchE. Our results go hand in hand with *(**Oyama et al., 2002**, **Abu-Taweel, 2016** and **Hussein et al., 2017)* who reported that the significant decrement in brain AchE activity of MSG-intoxicated rats when compared to healthy control rats. Elevation in neurotransmitters levels such as serotonin, dopamine, and glutamate in MSG control group was also supported previously (***Kristova et al., 1998***).

Intake of high doses of MSG causes glutamate(an excitatory amino acid) accumulation in synaptic junctions which may lead to overstimulation of glutamate receptors. This lead to persistent depolarization producing metabolic and functional exhaustion of the affected neurons and so causing neuronal necrosis and degeneration. Glutamate plays a key role in the regulation of blood–brain barrier permeability. Overstimulation of glutamate receptors in the cerebral capillaries would destabilize the blood–brain barrier (***Owoeye and Salami, 2017***). Increased glutamate level in the brain of rats exposed to MSG is similar to (***Kumaravel et al., 2012***). Over-expression of glutamate levels consequently lead to the breakdown of the blood–brain barrier and hippocampus and hypothalamus neurotoxicity (***Koenig et al., 1992***).

Significant increment in neurotransmitters like serotonin, dopamine, and glutamate levels in the cerebral cortex of MSG-intoxicated rats in comparison with healthy one were observed in our study. This serotonin finding was supported by a previous report that has shown changes of serotonin in different brain parts in rats exposed to MSG and aspartame (***Kristova et al., 1998 and Abu-Taweel, 2016)*** MSG acts on the glutamate receptors and releases neurotransmitters which play a vital role in normal physiological as well as pathological processes (***Abdallah et al., 2014***).

Bee venom and proplis administration, improved these results which might be attributed to their antioxidant properties that protect brain tissue and neurons.

Lee et al., (2012) reported that pretreatment of neuronal and microglial cells with BV significantly inhibited glutamate-mediated toxicity. The present results may have clinical implications and suggest that BV may be a potential treatment for the prevention of neurodegenerative diseases.

Propolis flavonoids are capable of scavenging free radicals and thereby protecting the cell membrane against lipid peroxidation and tissues against degeneration. Antioxidant and neuroprotective effects of propolis and its active components have been proved in many studies previously as reported by (***Alkis et al., 2015***). ***Da Silveira et al., (2016)*** explored the neurobehavioral and antioxidant effects of an ethanolic extract of yellow propolis (EEYP) that is due to its active constituents as triterpenoids, primarily lupeol and β-amyrin.

MSG- intake induced a state of oxidative stress in the rats brain tissue that evidenced by the significant elevation in brain oxidative stress markers as MDA (lipid peroxidation marker), NO , PCG as well as , 8-OHdG (marker of DNA oxidation) levels with a concomitant decrease in enzymatic and non-enzymatic antioxidants levels like decreased brain GSH level and reduction in the brain activities of SOD and CAT as well. These results go hand with hand with (***Gebicki, 2016***) who stated that free radicals formed in the brain tissue due to ingestion of MSG are known to cause deterioration of most proteins including enzymes. The attack of brain tissues by free radicals formed in sito, in combination with that diffused from circulation resulting from a defect in blood brain barriers , participate in the deleterious action on the brain enzymes.

Oxidative damage resulting from biochemical interactions between reactive oxygen species (ROS) and target biomolecules, such as nucleic acids, lipids, and proteins, is prominently linked to the etiology and progression of different oncologic and neurodegenerative diseases. DNA lesions indicator 8-OHdG have been identified as a biomarker of oxidative damage . The superoxide formation may promote peroxynitrite generation and protein nitration that may further result into oxidative damage to lipids, proteins and DNA oxidative stress lead to activation of inducible nitric oxide synthase activity (iNOS) causing massive increase in NO synthesis and lipid peroxidation leading to increased formation of MDA. Excess ROS can promote protein oxidation, forming protein carbonyls which have been described as reliable marker to estimate the degree of oxidant-mediated protein damage ***(Margetis et al., 2009).***

Overproduction of free radicals is mainly eliminated by antioxidant defense system including glutathione ,superoxide dismutase (SOD) and catalase. Deficiency in these antioxidants with relatively higher levels of free radicals and altered redox state induce a state of persistent oxidative stress that in turn lead to neurodegenerative diseases ***(Alkis et al., 2015)***

Our results revealed that both bee venom and proplis administration to rats intoxicated with MSG improved the oxidative status by decreasing the level of oxidative biomarkers and increasing the activity of the antioxidants enzymes CAT and SOD as well as GSH level and this go hand in hand with different studies ***(Alkis et al., 2015, Salman et al., 2015, Da Silveira et al., 2016 and Kocot et al., 2018)*** and this is due to their active components that act as strong antioxidants.

5. Conclusion

MSG is very dangerous and its use must be limited. MSG causes oxidative stress and affects brain badly. Bee products like bee venom and proplis are found to be very beneficial to health due to their active constituents that act as potent antioxidants. Apitherapy must be more researched and used on a large scale.

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