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Neuroprotective Evaluation of Extract of Ginger (*Zingiber officinale*) Root in Monosodium Glutamate-Induced Toxicity in Different Brain Areas Male Albino Rats

Abeer M. Waggas
Department of Zoology, Faculty of Girls Education,
Scientific Departments, Jeddah, Saudi Arabia

Abstract: In this study, the neuroprotective effect of the extract of ginger (*Zingiber officinale*) was investigated against MSG-induced neurotoxicity of male albino rat. The daily dose (4 mg kg^{-1} b.wt.) i.p. injection of pure monosodium glutamate (MSG) for 30 days and subsequent withdrawal caused a significant decrease in epinephrine (E), norepinephrine (NE), dopamine (DA) and serotonin (5-HT) content all tested areas (cerebellum, brainstem, striatum, cerebral cortex, hypothalamus and hippocampus) at most of the time intervals studied. This is may be due to activation of glutamate receptors, which led to increased the intracellular concentration of Ca^{+2} ions, so the release of neurotransmitters is increased and the content of monoamines is decreased. After the withdrawal, the decrease in monoamines levels remained in striatum, cerebral cortex and hypothalamus, this may be due to the region specific effect of monosodium glutamate. whereas, daily dose (100 mg kg^{-1} b.wt.) i.p., injection of Ginger *(Zingiber officinale)* root extract for 30 days and subsequent withdrawal caused a significant increased in epinephrine (E), norepinephrine (NE), dopamine (DA) and serotonin (5-HT) content all tested areas at most of the time intervals studied. This is may be due to inhibition of 5HT-3-receptor effects at the same time the extract blockade of Ca^{+2} channel, as result the release of neurotransmitter is decreased and the content is increased. After the extract withdrawal, the increase in monoamine levels remained in brainstem, striatum and hippocampus, this may be due to the region specific effect of the extract. The coadminisration of monosodium glutamate and ginger root extract caused increased in monoamine content in most of the tested brain areas at different time intervals. This is may be due to partly attributable to an antagonistic action of ginger root extracts on monosodium glutamate effect, so the monoamines content was increased. From these results, we can say that the ginger extract has a neuroprotective role against monosodium glutamate toxicity effect.

Key words: Ginger, glutamate, MSG, *Zingiber officinale*, neurotoxicity, brain areas, rat

INTRODUCTION

Glutamate is ubiquitous in nature and is presents in all living organisms. It is the principal excitatory neurotransmitter in central nervous system. Trade names of glutamate include monosodium glutamate (MSG), also known as sodium glutamate, umami, ajinamoto, vetsin and accent, is a sodium salt of non-essential amino acid glutamic acid (Kondoh and Torii, 2008). It is used as a food additive and is commonly marketed as a flavour enhancer for ever last 1200 years (Pavlovic *et al*., 2006). Many of the foods used in cooking for enhancing flavour contain high amount of glutamate in West African and Asian diets (Farmobi and Onyema, 2006). Glutamate in high doses produced neuroendocrine abnormalities (Moreno *et al*., 2005), neurodegeneration, neurotoxicity (Chaparro-Huerta *et al*., 2002) and oxidative damage in different organs (Farmobi and Onyema, 2006; Pavlovic *et al*., 2007).

Plant material in the human diet contain a large number of natural compounds, which may be of benefit in protecting the body against the development of neurotoxicity. One of the first plant with constituents reputed to possess neuroprotective properties was ginger (Lin *et al*., 2006).

Ginger *(Zingiber officinale)* is one of most widely used species of ginger family (Zingiberaceae) and is common condiment for various foods and beverages. Ginger has long history of medicinal use dating back 2.500 years in China and India for condition such as headaches, nausea and colds (Mowrey and Clayson, 1982; Grant and Lutz, 2000; Hickok *et al*., 2007).

Ginger extract have been extensively studied for a broad range of biological activities including anti-tumor (Surh *et al*., 1999), anti-convulsant, anxiolytic (Vishwakarma *et al*., 2002), treatment of Parkinson's disease (Kabuto *et al*., 2005), anti-inflammatory (Grzanna *et al*., 2005), anti-bacterial (Hoffman, 2007) and anti-diabetic (Islam and Choi, 2008).

Recently, medical researchers have verified that ginger contain many active substances which actually share in keeping body health. The bioactive components of *Zingiber officinale* were characterized by spectroscopic analysis as zingerone, gingerdione,

dehydrozingerones which exhibited potent antioxidant, 1'-acetoxychavicol acetate (ACA) and volatile oil (Kuo *et al*., 2005; Lin *et al*., 2006; Campbell *et al*., 2007; Riyazi *et al*., 2007).

Consequently, the present study analyzes the extent of neurochemicaldamage to several monoaminergic systems by evaluating the changes in epinephrine (E), norepinephrine (NE), dopamine (DA) and serotonin (5-TH) content in different brain region after treatment with monosodium glutamate in different brain region (cerebellum, brainstem, striatum, cerebral cortex, hypothalamus and hippocampus) and evaluate the role of ginger extract as a protective agent against monosodium glutamate neurotoxicity.

MATERIALS AND METHODS

The root of ginger (*Zingiber officinale*) and monosodium glutamate were obtained from the open market in Jeddah, Saudi Arabia, through July 2008.

Preparation of the plant extract

Aqueous extract: The root of ginger was washed and cut into pieces. It was weighed (100 g) and cold distilled water poured into it to give a final volume of 200 mL. The herb was allowed to souk for 8 h and heated to just below boiling point for 20 min before cooling (York *et al*., 2007). The contents were filtered and used for study.

Animals: Experiments were performed on adult male albino rats, *Rattus rattus* (120-140 g), 8-10 weeks old. Animals were reared in animal house at the center of king Fahad of medical researchers in Jeddah, Saudi Arabia. An adequate diet and water were allowed *ad libitum* under standard conditions of light, humidity and temperature (22-25°C). The treated animals were randomly divided into five groups.

The first group (n = 24) was divided into four subgroups each of 6 rats. The animals were daily injected with single dose (i.p.) of with 4 mg kg^{-1} of monosodium glutamate (Moreno *et al*., 2006; Pavlovic *et al*., 2006) and one subgroup was decapitated after 10, 20 and 30 days. To examine the withdrawal effect, the animals were decapitated after 10 days of stopping the administration of monosodium glutamate. The second group (n = 24) was divided as the first group but the rats were daily injected with single dose of 100 mg kg^{-1} of ginger (*Zingiber officinale* Roscoe) root extract (Datta and Sukul, 1987; Huang *et al*., 1990; Gupta and Sharma, 2002; Ojewole, 2006). The 3rd group (n = 24) divided as the first group but the rats were daily injected with single dose of ginger root extract (100 mg kg^{-1} i.p.) and monosodium glutamate (4 mg kg^{-1} i.p.). The 4th group (n = 6) was injected daily with ginger root extract (100 mg kg^{-1} i.p.) for 15 days then injected with monosodium glutamate (4 mg kg^{-1} i.p.) for 15 days. The 5th group divided as the first group, the rats were injected with saline vehicle and served as control.

The rats were killed by sudden decapitation at the designed times. The brain was rapidly and carefully excised and then was dissected on dry ice glass plate according the method of Glowinski and Iversen (1966) into the following regions: cerebellum, brainstem, striatum, cerebral cortex, hypothalamus and hippocampus. The brain tissues were wiped dry with a filter paper, weighed, wrapped in plastic films and then in aluminum foil and quickly frozen in dry ice pending analysis.

Epinephrine (E), norepinephrine (NE), dopamine (DA) and serotonin (5-HT) were extracted and estimated according to the method of Chang (1964) modified by Ciarlone (1978). The fluorescence was measured in Jenway 6200 fluorometer.

Statistical analysis: The data are presented as Mean±SE. Statistical analysis between control and treated animals were performed by using Student's t-test. Mean were considered significantly different for $p<0.05$ (Hill, 1971). Percentage difference is representing the percent of variation with respect to the control.

RESULTS

Table 1 shows that the injection of 4 mg kg^{-1} (i.p.) of monosodium glutamate caused a significant decrease E content in hypothalamus after 10 days and in striatum, cerebral cortex and hypothalamus after 20 days. A decrease was also found in all tasted areas after 30 days except in brain stem. The significant decrease in E content persisted for 10 days of withdrawal in striatum, cerebral cortex and hypothalamus.

As shown in Table 2, 4 mg kg^{-1} (i.p.) of monosodium glutamate and its subsequent withdrawal produced a significant decrease in NE content in hypothalamus after 10 days. The NE content still significant decrease after 20 and 30 days in all tasted after 20 and 30 days except in brain stem and hippocampus after 20 days and in brain stem after 30 days. The significant decrease in NE content persisted for 10 days of withdrawal in striatum, cerebral cortex and hypothalamus.

Table 3 shows that 5 mg kg^{-1} (i.p.) of monosodium glutamate and its subsequent withdrawal produced a significant decrease in DA content at all tested times in all the tested brain areas except in cerebellum, brainstem and hippocampus after 10 days and in hippocampus after 20 days. The significant decrease in DA content persisted for 10 days of withdrawal in striatum, cerebral cortex and hypothalamus.

Table 1: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and its subsequent withdrawal on epinephrine (E) content (μg g^{-1}) in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	312.21±9.31	813.32±13.31	701.12±18.31	123.01±1.12	801.59±19.31	631.41±10.12
	T	330.52±54.36	757.65±13.25	655.36±23.21	112.35±1.02	713.32±18.36	612.35±12.36
		5.86	-6.84	-6.52	-8.66	-11.01*	-1.59
20%	C	301.81±10.11	899.81±10.74	788.31±17.38	128.11±1.01	833.33±17.81	666.31±19.31
	T	281.32±15.24	814.35±13.33	705.36±19.32	108.36±1.32	716.36±20.32	645.32±11.36
		-6.78	-9.49	-10.52*	-15.41*	-14.03*	-3.15
30%	C	311.81±17.11	877.31±20.18	727.15±18.33	127.13±1.00	836.66±15.31	612.16±13.33
	T	268.32±13.33	791.36±18.64	626.36±14.36	111.36±0.54	710.65±18.88	530.21±18.25
		-13.94*	-9.79	-13.86*	-12.40*	-15.06*	-13.38*
Withdrawal							
10%	C	342.11±11.11	833.33±18.31	730.05±14.31	122.31±1.32	808.89±16.61	615.31±19.88
	T	337.65±15.26	845.33±18.45	656.35±17.45	108.11±1.32	718.65±14.65	625.31±15.12
		-1.3	1.44	-10.09*	-11.60*	-11.15*	1.62

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 2: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and its subsequent withdrawal on norepinephrine (NE) content (μg g^{-1}) in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	315.25±11.52	847.59±20.24	714.35±21.54	124.35±1.54	814.26±18.25	634.26±15.26
	T	292.36±16.66	763.36±12.22	689.94±20.12	112.32±1.00	723.36±20.67	625.58±18.54
		-7.26	-9.93	-3.41	-9.67	-11.16*	-1.36
20%	C	325.35±11.25	853.36±14.25	714.35±20.34	127.79±1.11	822.35±19.54	694.35±15.56
	T	291.35±17.54	833.36±16.35	635.76±18.45	110.36±1.03	719.65±17.77	655.36±18.64
		-10.45*	-2.34	-11.00*	-13.63*	-12.48*	-5.61
30%	C	333.35±10.25	852.36±18.36	725.68±18.54	126.35±0.54	807.95±16.32	679.35±15.75
	T	284.23±15.87	821.36±14.44	612.32±19.64	110.98±1.05	701.32±18.88	606.66±17.75
		-14.73*	-3.63	-15.62*	-12.16*	-13.19*	-10.69*
Withdrawal							
10%	C	328.94±14.85	879.56±10.14	745.85±13.54	121.65±1.01	816.65±17.25	686.66±15.35
	T	311.36±11.12	866.66±16.65	649.64±13.31	105.36±0.32	723.36±17.54	695.32±20.32
		-5.34	-1.46	-12.89*	-13.39*	-11.42*	1.26

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 3: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and its subsequent withdrawal on dopamine (DA) content (μg g^{-1}) in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	355.54±11.25	834.68±18.25	745.84±20.54	120.87±1.05	864.79±16.87	677.89±10.47
	T	335.65±16.66	789.35±12.36	633.36±21.36	105.36±1.12	756.65±19.65	689.35±11.35
		-5.59	-5.43	-15.08*	-12.84*	-12.50*	1.69
20%	C	364.55±14.87	845.67±17.84	758.94±17.84	131.87±1.11	839.38±19.54	666.66±14.58
	T	321.85±15.35	757.19±18.84	673.94±13.65	115.36±1.22	725.24±17.25	645.35±11.04
		-11.71*	-10.46*	-11.19*	-12.51*	-13.59*	-3.19
30%	C	344.52±13.65	867.54±17.77	725.54±18.88	124.57±1.02	825.34±16.25	685.21±14.25
	T	304.88±12.22	777.25±16.44	625.36±15.55	108.32±1.03	715.46±12.02	615.55±17.36
		-11.50*	-10.40*	-13.80*	-13.04*	-13.31*	-10.16*
Withdrawal							
10%	C	363.33±14.25	846.44±18.88	727.25±11.21	125.35±0.89	802.31±1.12	679.25±9.35
	T	342.36±14.94	825.65±17.65	635.65±14.64	109.74±0.54	717.54±13.33	666.54±12.32
		-5.77	-2.45	-12.59*	-12.45*	-10.56*	-1.87

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Moreover, the treatment significantly decrease the 5-HT content at all tested times in all the tested brain areas except in cerebellum, brain stem and hippocampus after 10 days. The 5-HT content still significantly decreased 10 days after withdrawal in striatum, cerebral cortex and hypothalamus (Table 4).

The single daily i.p. injection of 100 mg kg^{-1} of ginger (*Zingiber officinale*) root extract significantly increase

E content at all tested times in all tested brain areas except in brain stem after 10 days, in cerebral cortex and hypothalamus after 10 and 20 days. The E content still significantly increased 10 day after withdrawal of the extract in all tested areas except in cerebral cortex and hypothalamus (Table 5).

Table 6 shows that, the treatment of ginger (*Zingiber officinale*) root extract induced a significant increase in NE at all tested times in all the tested brain areas except in cerebellum after 10 and 20 days and in brain stem and hypothalamus after 10 days. The NE content persisted in its significant increase 10 days after the withdrawal of extract in brain stem, striatum and hippocampus.

There was a significant increase in DA content at all tested times in all tested brain areas except in brainstem and hypothalamus after 10 days and cerebral cortex after 10 and 20 days. The withdrawal of the extract caused a significant increase in DA content in brain stem, striatum and hippocampus (Table 7).

Moreover, the treatment of the extract significantly increase the 5-HT content at all tested times in all the tested brain areas except in brain stem and hypothalamus after 10 days and in cerebral cortex after 10 and 20 days. The significant increase in 5-HT content persisted for 10 days of withdrawal in brain stem, striatum and hippocampus (Table 8).

The coadministration of 4 mg kg^{-1} (i.p.) monosodium glutamate and 100 mg kg^{-1} (i.p.) of ginger (*Zingiber officinale* Roscoe) root extract for 30 day induced a significant increase in E content in cerebellum and hippocampus after 10 days. The increase in E content also found in all tasted areas after 20 and 30 days except in brain stem after 20 days and in cerebral cortex after 20 and 30 days. The E content still significantly increased after withdrawal in all tested areas except in brain stem and cerebral cortex (Table 9).

Table 10 shows that the treatment induced a significant increase in NE content in all tested areas after 10, 20 and 30 day except in cerebellum, brain stem and

Table 4: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and its subsequent withdrawal on serotonin (5-TH) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	315.25±8.25	883.25±15.22	748.32±14.44	128.32±1.22	826.36±12.22	643.25±14.25
	T	288.54±12.35	832.77±11.02	656.36±20.21	112.45±1.02	722.35±13.32	603.44±7.14
		-8.47	-5.71	-12.28*	-12.36*	-12.58*	-6.18
20%	C	352.21±9.78	897.36±17.77	764.35±14.65	127.36±1.00	846.35±16.36	695.88±17.64
	T	290.35±14.65	802.74±13.32	656.65±14.96	111.32±0.44	747.84±9.54	607.11±8.22
		-17.56*	-10.57*	-14.09*	-12.59*	-11.63*	-12.75*
30%	C	369.32±15.25	876.36±17.77	743.32±18.69	124.32±1.05	802.32±18.25	683.33±18.24
	T	264.58±17.85	765.25±11.47	627.65±12.31	106.44±1.66	708.46±7.15	608.25±14.22
		-28.36*	-12.67*	-15.56*	-14.38*	-11.69*	-10.98*
Withdrawal							
10%	C	322.55±15.25	847.25±20.35	744.35±16.55	124.44±0.84	821.35±14.96	643.36±13.33
	T	309.67±15.21	833.33±17.11	638.46±14.01	109.45±1.77	719.55±11.44	653.24±8.88
		-3.99	-1.64	-14.22*	-12.04*	-11.95*	1.53

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 5: Effect of chronic administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on epinephrine (E) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	332.21±9.31	813.32±13.31	701.12±18.31	123.01±1.12	801.59±19.31	631.41±10.12
	T	374.25±12.35	859.36±21.35	794.35±13.25	120.35±0.25	823.35±11.98	717.26±12.32
		12.65*	5.71	13.29*	-2.35	2.71	13.59*
20%	C	301.81±10.11	829.81±10.74	728.31±17.38	120.11±1.01	833.33±17.81	666.31±19.31
	T	376.94±8.012	929.35±14.64	818.69±16.32	131.02±1.25	889.46±15.64	739.54±14.87
		24.89*	11.99*	12.40*	9.08	6.76	10.99*
30%	C	331.81±17.11	817.31±20.18	727.15±18.33	121.13±1.00	826.66±15.31	612.16±13.33
	T	388.46±9.64	933.21±12.78	818.65±14.44	138.32±1.12	919.87±15.66	733.64±15.55
		17.12*	14.18*	12.58*	14.19*	11.27*	19.84*
Withdrawal							
10%	C	312.11±11.11	813.33±18.31	730.05±14.31	122.31±1.32	808.89±16.61	615.31±19.88
	T	350.24±7.54	898.65±16.44	833.65±17.66	130.25±0.54	866.32±18.64	691.76±11.79
		12.17*	10.49*	11.45*	6.49	7.09	12.42*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 6: Effect of chronic administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on norepinephrine (NE) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		----------μg g^{-1}±SE----------					
Treatment							
10%	C	365.25±11.52	827.59±20.24	714.35±21.54	124.35±1.54	824.26±18.25	634.26±15.26
	T	381.35±8.46	887.45±18.64	786.54±11.81	139.65±0.33	894.65±12.55	711.36±7.77
		4.4	7.23	10.10*	12.30*	8.53	12.15*
20%	C	325.35±11.25	829.16±14.25	744.35±20.34	121.79±1.11	812.35±19.54	634.35±15.56
	T	388.46±11.47	923.36±10.25	838.36±8.45	139.44±1.08	898.76±17.22	707.55±11.46
		9.39	11.36*	12.62*	14.49*	10.63*	11.53*
30%	C	333.35±10.25	812.36±18.36	745.68±18.54	122.35±0.54	847.95±16.32	639.35±15.75
	T	415.97±10.24	933.33±17.54	833.77±10.77	138.77±0.33	950.22±11.55	733.55±17.15
		24.78*	14.89*	11.81*	13.42*	12.06*	14.73*
Withdrawal							
10%	C	328.94±14.85	829.56±10.14	725.85±13.54	124.65±1.01	816.65±17.25	636.66±15.35
	T	354.56±14.21	917.88±12.44	824.55±8.44	127.25±1.11	862.25±13.33	715.62±10.22
		7.78	10.64*	13.18*	2.08	5.58	12.40*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 7: Effect of chronic administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on dopamine (DA) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		----------μg g^{-1}±SE----------					
Treatment							
10%	C	325.54±11.25	854.68±18.25	745.84±20.54	124.87±1.05	864.79±16.87	657.89±10.47
	T	364.23±10.25	905.48±20.22	856.44±15.85	135.21±1.11	904.68±20.21	732.54±16.47
		11.88*	5.94	14.82*	8.28	4.61	11.34*
20%	C	334.55±14.87	865.67±17.84	738.94±17.84	128.87±1.11	859.38±19.54	666.66±14.58
	T	391.78±11.77	973.54±12.84	839.55±11.22	139.32±0.23	956.11±17.69	760.55±13.11
		17.10*	12.46*	13.61*	8.1	11.25*	14.08*
30%	C	344.52±13.65	817.54±17.77	755.54±18.88	121.57±1.02	835.34±16.25	655.21±14.25
	T	404.22±13.32	910.45±12.33	844.21±15.41	138.12±0.98	927.65±12.46	771.25±20.47
		17.32*	11.36*	11.73*	13.61*	11.05*	17.71*
Withdrawal							
10%	C	333.33±14.25	846.44±18.88	757.25±11.21	125.35±0.89	842.31±11.12	659.25±9.35
	T	354.22±12.32	951.74±14.57	854.66±17.46	130.22±1.28	913.78±10.95	740.35±10.11
		6.26	12.44*	12.86*	3.88	8.48	12.30*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 8: Effect of chronic administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on serotonin (5-TH) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		----------μg g^{-1}±SE----------					
Treatment							
10%	C	315.25±8.25	843.25±15.22	748.32±14.44	128.32±1.22	846.36±12.22	643.25±14.25
	T	371.47±12.21	886.74±12.44	856.33±11.87	131.25±1.23	891.35±12.36	756.32±12.35
		17.83*	5.15	14.43*	2.28	5.31	18.97*
20%	C	352.21±9.78	837.36±17.77	724.35±14.65	127.36±1.00	846.35±16.36	645.88±17.64
	T	444.57±7.64	925.87±15.85	855.54±11.02	132.36±0.24	933.87±17.84	784.25±19.35
		26.22*	10.57*	18.11*	3.92	10.34*	20.03*
30%	C	369.32±15.25	866.36±17.77	733.32±18.69	125.32±1.05	822.32±18.25	633.33±18.24
	T	470.32±10.87	968.33±21.35	825.45±10.22	138.64±1.89	923.35±20.44	764.32±13.25
		27.34*	11.76*	12.56*	10.62*	12.28*	20.68*
Withdrawal							
10%	C	322.55±15.25	847.25±20.35	764.35±16.55	124.44±0.84	841.35±14.96	643.36±13.33
	T	342.99±9.63	936.63±10.89	868.64±18.55	129.63±1.06	913.65±18.74	745.35±10.29
		6.33	10.54*	13.64*	4.17	8.23	15.85*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

cerebral cortex after 10 days. The NE content persisted in its significant increase 10 days after the withdrawal of coadministration of 4 mg kg^{-1} (i.p.) monosodium glutamate and 100 mg kg^{-1} (i.p.) of ginger (*Zingiber officinale*) root extract in striatum, hypothalamus and hippocampus.

There was a significant increase in DA content at all tested times in all the tested brain areas except in brain

stem and cerebral cortex after 10 and 20 days and in striatum after 10 days. The significant increase in DA content persisted for 10 days of the withdrawal in striatum, hypothalamus and hippocampus (Table 11).

Moreover, the treatment with 4 mg kg^{-1} (i.p.) of monosodium glutamate and 100 mg kg^{-1} (i.p.) of ginger (*Zingiber officinale*) root extract significantly increased 5-HT content at all tested times in all the tested brain

Table 9: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on epinephrine (E) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	332.21±9.31	813.32±13.31	701.12±18.31	123.01±1.12	801.59±19.31	631.41±10.12
	T	386.62±12.54	859.66±18.64	765.64±16.55	125.36±0.88	823.36±11.32	707.95±11.87
		16.37*	5.69	9.2	1.91	2.71	12.12*
20%							
	C	301.81±10.11	899.81±10.74	728.31±17.38	120.11±1.01	833.33±17.81	666.31±19.31
	T	354.89±11.89	933.63±11.78	805.22±19.33	126.33±1.41	937.99±19.32	733.59±20.22
		17.58*	3.75	10.56*	5.17	12.55*	10.09*
30%							
	C	331.81±17.11	877.31±20.18	737.15±18.33	121.13±1.00	836.66±15.31	612.16±13.33
	T	402.36±15.66	985.64±18.66	825.79±19.31	123.49±0.25	942.45±20.87	715.45±11.25
		21.26*	12.34*	12.02*	1.94	10.57*	16.87*
Withdrawal							
10%	C	302.11±11.11	833.33±18.31	730.05±14.31	122.31±1.32	808.89±16.61	635.31±19.88
	T	349.64±10.77	879.65±14.66	826.97±10.24	120.31±0.56	892.69±13.55	723.01±10.25
		15.73*	5.52	13.27*	-1.63	10.35*	13.80*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 10: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on norepinephrine (NE) content (μg g^{-1}) in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	365.25±11.52	847.59±20.24	714.35±21.54	124.35±1.54	854.26±18.25	634.26±15.26
	T	380.23±12.88	890.35±17.02	818.32±20.36	135.36±1.55	943.65±17.63	733.36±18.25
		4.1	5.04	14.55*	8.85	10.46*	15.62*
20%	C	325.35±11.25	853.36±14.25	764.35±20.34	121.79±1.11	812.35±19.54	694.35±15.56
	T	380.96±10.87	939.65±16.88	846.09±17.54	138.74±1.08	939.74±13.58	794.63±20.87
		17.09*	10.11*	10.69*	13.91*	15.68*	14.44*
30%	C	333.35±10.25	852.36±18.36	745.68±18.54	122.35±0.54	847.95±16.32	679.35±15.75
	T	404.02±10.08	945.76±17.54	850.99±12.54	137.69±1.30	957.03±19.11	796.78±16.55
		21.19	10.95*	14.12*	12.23*	12.86*	17.28*
Withdrawal							
10%	C	328.94±14.85	879.56±10.14	745.85±13.54	124.65±1.01	866.65±17.25	666.66±15.35
	T	344.61±8.14	955.33±12.87	836.39±14.50	136.04±0.08	956.36±1.84	751.77±12.02
		4.76	8.6	12.13*	9.13	10.35*	12.76*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test %: Percentage of change from control. *Significant at $p<0.05$

Table 11: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on dopamine (DA) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	325.54±11.25	854.68±18.25	745.84±20.54	124.87±1.05	864.79±16.87	677.89±10.47
	T	391.25±9.35	888.65±14.78	815.95±11.87	129.65±0.12	968.36±16.87	773.68±11.87
		20.18*	3.97	9.4	3.82	11.97*	14.13*
20%	C	364.55±14.87	895.67±17.84	778.94±17.84	128.87±1.11	859.38±19.54	666.66±14.58
	T	415.98±9.65	923.87±16.55	887.91±11.05	138.95±0.23	966.63±20.24	791.22±11.57
		14.10*	3.14	13.98*	7.82	12.74*	18.68*
30%	C	344.52±13.65	857.54±17.77	755.54±18.88	120.57±1.02	835.34±16.25	655.21±14.25
	T	438.94±12.58	960.74±10.87	866.44±10.22	138.22±0.66	971.71±14.22	780.75±14.77
		17.40*	12.03*	14.67*	14.63*	16.32*	19.16*
Withdrawal							
10%	C	333.33±14.25	846.44±18.88	777.25±11.21	125.35±0.89	842.31±1.12	679.25±9.35
	T	358.94±8.77	909.78±11.54	867.32±13.55	134.22±1.02	933.36±10.21	762.88±15.77
		7.68	7.48	11.28*	7.07	10.80*	12.31*

Statistical analyses were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 12: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) and its subsequent withdrawal on serotonin (5-TH) content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	315.25±8.25	843.25±15.22	748.32±14.44	128.32±1.22	846.36±12.22	643.25±14.25
	T	371.32±13.22	891.22±10.87	833.36±10.84	129.32±1.22	939.87±12.54	740.25±11.58
		17.78*	5.68	11.36*	0.77	11.04*	15.07*
20%	C	352.21±9.78	877.36±17.77	764.35±14.65	127.36±1.00	846.35±16.36	645.88±17.64
	T	405.36±8.54	928.36±14.01	888.76±16.77	136.58±0.11	966.74±14.55	779.54±13.65
		15.09*	5.81	16.27*	7.23	14.22*	20.69*
30%	C	369.32±15.25	866.36±17.77	793.32±18.69	125.32±1.05	822.32±18.25	633.33±18.24
	T	446.35±10.21	957.84±15.00	891.77±18.44	134.68±1.04	955.66±17.44	741.55±10.87
		20.85*	10.55*	12.40*	7.46	16.21*	17.08*
Withdrawal							
10%	C	322.55±15.25	847.25±20.35	764.35±16.55	124.44±0.84	861.35±14.96	643.36±13.33
	T	361.85±7.52	933.65±11.77	854.69±10.24	131.87±1.08	915.87±17.74	730.36±11.5
		12.18*	10.19*	11.81*	5.97	6.32	13.52*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 13: Effect of chronic administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) for 15 days then administration with monosodium glutamate (4 mg kg^{-1}, i.p.) for 15 days on E, NE, DA, 5-HT content in different brain areas of male albino rat

Time of area decapitation (day)		Cerebellum	Brainstem	Striatum	Cerebral cortex	Hypothalamus	Hippocampus
		μg g^{-1}±SE					
Treatment							
10%	C	351.81±17.11	877.31±20.18	777.15±18.33	121.13±1.00	866.66±15.31	612.16±13.33
	T	415.65±12.25	908.36±14.25	833.65±10.89	138.65±0.29	958.36±16.39	746.39±14.89
		18.14*	3.53	7.27	14.46*	10.58*	21.92*
20%	C	333.35±10.25	852.36±18.36	745.68±18.54	122.35±0.54	847.95±16.32	679.35±15.75
	T	388.36±9.54	933.65±12.35	819.47±10.27	137.08±1.25	935.23±11.44	759.16±15.22
		16.50*	9.53	9.89	12.03*	10.29*	11.74*
30%	C	344.52±13.65	897.54±17.77	755.54±18.88	124.57±1.02	835.34±16.25	655.21±14.25
	T	408.23±8.14	989.37±14.55	816.35±12.35	133.5±1.07	925.44±10.29	733.16±10.05
		18.49*	10.23*	8.04	7.16	10.78*	11.89*
Withdrawal							
10%	C	369.32±15.25	866.36±17.77	753.32±18.69	125.32±1.05	822.32±18.25	633.33±18.24
	T	425.36±8.9	954.54±11.8	833.33±17.89	129.67±1.00	913.64±17.85	725.67±13.55
		15.17*	10.17*	10.62*	3.47	11.10*	14.58*

Statistical analysis were performed between control (C = 6) and treated (T = 6) animals by using paired t-test. %: Percentage of change from control. *Significant at $p<0.05$

Table 14: Effect of chronic administration of monosodium glutamate (4 mg kg^{-1}, i.p.) and ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) on total body weight (g) of male albino rat

	Total body weight			
Time of decapitation (%)	Control	Monosodium glutamate (4 mg kg^{-1})	Ginger (100 mg kg^{-1})	Ginger (100 mg kg^{-1})+ monosodium glutamate (4 mg kg^{-1})
10 days	121.33±3.17	142.50±9.08	108.00±8.60	131.83±9.07
		17.44*	-10.98*	8.65
20 days	122.33±1.47	148.50±2.74	101.06±1.81	130.50±2.77
		21.39*	-17.76*	6.67
30 days	132.66±3.09	162.66±6.38	106.33±1.40	145.00±2.75
		22.61*	-19.84*	9.3
10 days withdrawal	140.50±1.99	155.50±2.30	122.00±4.50	149.66±2.23
		10.67*	-13.16*	6.51

areas except in brain stem after 10 and 20 days and in cerebral cortex after 10, 20 and 30 days. The 5-HT content still significantly increased after withdrawal in all tested areas except in cerebral cortex and hypothalamus (Table 12).

Table 13 shows that administration of ginger (*Zingiber officinale*) root extract (100 mg kg^{-1}, i.p.) for 15 days then administration with monosodium glutamate (4 mg kg^{-1}, i.p.) for 15 days caused a significant increased in E and NE content in cerebellum, cerebral cortex, hypothalamus and hippocampus. There was a significant increase in DA content in cerebellum, brain stem, hypothalamus and hippocampus and a significant increase in 5-HT content in cerebellum, brain stem, striatum, hypothalamus and hippocampus.

As shown in Table 14, 4 mg kg^{-1} (i.p.) of monosodium glutamate and its subsequent withdrawal produced a significant increase in total body weight (g)

at different time intervals. Whereas there was a significant decrease in total body weight (g) at different time intervals in treated rat with 100 mg kg^{-1} of ginger (*Zingiber officinale*) root extract.

DISCUSSION

Treatment with glutamate as monosodium glutamate (MSG) induced severe neurochemical damage and neurotoxic effects on some brain regions (Johnston *et al*., 1984; Ortuno-Sahagun *et al*., 1997; Ortiz *et al*., 2006). Various investigators have previously demonstrated some of the neurotoxicological signs induced by monosodium glutamate intake. These neurotoxicological signs are observed after the administration of monosodium glutamate (4 mg kg^{-1} wt. i.p.) in mouse and rats, including hypoxia-ischemia, hepatotoxicity, musculoskeltal pain and metabolic failures (Pavlovic *et al*., 2007). Excessive accumulating of glutamate in the synaptic cleft has been associated with axcitotoxicity and glutamate is implicated in number of neurological disorder (Mallick, 2007). However, there is accumulating evidence suggesting that glutamate-induced toxicity can be mediated through necrosis and apoptosis (Ankarcrona *et al*., 1995; Martin *et al*., 2000).

The principle of modulating toxic effect of MSG by interfering with its neurotransmitter role may have significant impact on the understanding neurodegenerative disorders. Wallace and Dawsons (1990) cited that, monosodium glutamate altered neurotransmitter content in discrete brain regions of adult male rats. Several lines of evidence indicate that treatment with monosodium glutamate induced decreased in the brain levels of DA, NE, E and 5-HT and the primary metabolites of these monoamines in some brain regions (Yoshida *et al*., 1984; Nakagawa *et al*., 2000; Lombardi *et al*., 2004). These changes are associated with increase in body weight (Oida *et al*., 1984; Camihort *et al*., 2005; Moreno *et al*., 2006) and decrease in spontaneous motor activity (Sun *et al*., 1993; Nakagawa *et al*., 2000).

From the present result it is clear that the chronic administration of monosodium glutamate (4 mg kg^{-1} i.p.) and its subsequent withdrawal caused a significant decrease in monoamines content in most of the tested brain areas at different time intervals. The earlier studies indicated that treatment of MSG caused a significant reduction in DA level, the increase in the number of DA receptors is probably direct effect of reduced DA levels after treatment with MSG (Heiman and Ben-Jonathan, 1983; Heal *et al*., 1992). Wortley *et al*. (1999) and Nakagawa *et al*. (2000) reported that, hypothalamic and cortex levels of NE, DA, 5-HT and their metabolites in the MSG group were lower than in the normal group in rats, which may be in part, due to activation of glutamate receptors (Gill *et al*., 2000; Martin *et al*., 2000; Pavlovic *et al*., 2007) which increasing the intracellular Ca^{+2} ions (Boldyrev *et al*., 2004; Lombardi *et al*., 2004). These changes are associated with decrease in food intake and an increase in adipose tissue mass (Stricker-Krongrad *et al*., 1992), the MSG-obese rats appear to be attributable to the destruction of the ventromedial nucleus (VMH), the satiety center and the lateral hypothalamic areas (LH), the food intake center, just appetite in the hypothalamus (Lorden and Caudle, 1986; Ganong, 1990; Stricker-Krongrad *et al*., 1992).

From the earlier studies and the present results, it could be concluded that the chronic administration of monosodium glutamate decreased the monoamines content in most of the tested brain areas at different time intervals, this is may be due to activation of glutamate receptors, which led to increased the intracellular Ca^{+2} ions, so the release of neurotransmitters is increased and the content of monoamines is decreased. From the present result it is also clear that, after the withdrawal of MSG, there are regional differences in its effect. The most affected areas are striatum which is a brain region responsible for motor activity, cerebral cortex which is responsible for motor (Chaparro-Huerta *et al*., 2002) and hypothalamus which is responsible for appetite, body temperature, water balance and sleep (Bloom, 2001). Wortley *et al*. (1999) demonstrated that the effect of MSG was specific. So, there were disturbances in the spontaneous motor activity and increase in body weight. These results are agreement with the study carried out by Nakagawa *et al*. (2000) and Ortiz *et al*. (2006).

Ginger extract possesses antioxidative characteristic, since it can scavenge superoxide anion and hydroxyl radicals (Cao *et al*., 1993; Krishnakantha and Lokesh, 1993; El-Abhar *et al*., 2008). Ginger contains a number of pungent constituent and active ingredients. The major pungent compounds in ginger, from studies of lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone and paradol (Govindarajan, 1982). The compound 6-gingrol appears to be responsible for its characteristic taste (Grant and Lutz, 2000). The compounds 6-gingerol and 6-shogaol have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effect (Suekawa *et al*., 1984). Lin *et al*. (2006) indicated that 1-(3, 4-dimethoxyphenyl)-3, 5-dodecenedione (I(6)), a derivative of gingerdione mediated neuroprotective effect due to increasing phosphorylation levels of extracellular signal-regulated kinases (ERKs).

Various investigators (Huang *et al*., 1990; Abdel-Aziz *et al*., 2006; Riyazi *et al*., 2007) have previously demonstrated that extract of ginger and its fractions have anti -5HT3-receptor effects.

5-HT3 receptor stimulation contributes to fast excitatory synaptic transmission in the central nervous system (Sugita *et al*., 1992; Férézou *et al*., 2002) and also modulates the release of several neurotransmitters including acetylcholine, cholecystokinin, dopamine, glutamate, norepinephrine and particularly γ-aminobutyric acid, the exocytosis of which is enhanced by direct Ca^{2+} influx through the ionophore of presynaptic 5-HT3 receptors (Chameau and Van-Hooft, 2006; Fink and Göthert, 2007). Also, Ghayur *et al*. (2005) found that aqueous extract from ginger (3.0-10.0 mg kg^{-1}) in guinea-pig caused Ca^{+2} antagonists activity (Blockade of Ca^{+2} channel). Zingerone and other derivatives from ginger inhibits the release of most neurotransmitter especially serotonin (Marles *et al*., 1992; Hasenohrl *et al*., 1996) and dopamine (Kabuto *et al*., 2005). These changes are associated with weight loss via., inhibition cholesterol biosynthesis (Tanabe *et al*., 1993; Greenway *et al*., 2006) and hypothermia via., an inhibitory effect on metabolic with no change in physical activity (Ueki *et al*., 2008). Brainstem, striatum and hippocampus were most affected areas, where brainstem is region that plays a vital role in basic attention, arousal, nausea and consciousness. Levine *et al*. (2008) cited that ginger reduced the delayed nausea of chemotherapy and reduced use of antiemetic medications. Striatum is a brain region that controls activity; this is in agreement with the study carried out by Kabuto *et al*. (2005) which demonstrated that the extract of ginger caused dopamine (DA) reduction release in mouse striatum. And hippocampus which is responsible for memory, ginger extract alterations in spatial learning and memory (Topic *et al*., 2002).

From the present results and earlier studies it could be concluded that the increase in the monoamines content in the tested brain areas after the chronic administration of 100 mg kg^{-1} (i.p.) of ginger (*Zingiber officinale*) root extract may be due to inhibition of $5HT_3$-receptor effects at the same time the extract blockade of Ca^{+2} channel, as result the release of neurotransmitter is decreased and the content is increased.

The coadninisration of monosodium glutamate and ginger root extract caused increased in monoamine content in most of the tested brain areas at different time intervals. This is may be due to partly attributable to an antagonistic action of ginger root extracts on monosodium glutamate effect, so the monoamines content was increased. This effect was clear in the present study specially in animal group that received ginger root extract (100 mg kg^{-1} i.p.) for 15 days then treatment with monosodium glutamate (4 mg kg^{-1} i.p.) for 15 days; these group showed improvement in monoamines content compared with animal group that received monosodium glutamate.

In conclusion, the present study showed that the neuro chemical damage of the brain areas, caused a decreased in monoamines content under the effect of monosodium glutamate can be minimized by ginger root extract which improve content of monoamines deferent brain areas.

REFERENCES

Abdel-Aziz, H., T. Windeck, M. Ploch and E.J. Verspohl, 2006. Mode of action og gingerols and shogaols on 5-HT3 receptors: Binding studies, cation uptake by the receptors channel and contraction of isolated guinea-pig ileum. Eur. J. Pharmacol., 530: 136-143.

Ankarcrona, M., J.M. Dypbukt, E. Bonfoco, B. Zhivotovsky, S. Orrenius, S.A. Lipton and P. Nicotera, 1995. Glutamate-induced neuronal death: A succession of nicrosis or apoptosis depending on mitochondrial function. Neuron, 15: 961-973.

Bloom, F.E., 2001. Neurotransmission and the Central Nervous System. In: The Pharmacological Basis of Therapeutics, 9th Edn., Hardmann, G.L., L.E. Limbird, P.B. Molinoff, R.W. Ruddon and A.G. Gilman (Eds.). McGraw-Hill, New York, pp: 267-290.

Boldyrev, A.A., V.I. Kazey, T.A. Leinsoo, A. Maskina, O. Tyulina and P. Johnson *et al*., 2004. Rodent lymphocytes express functionally active glutamate receptors. Biochem. Biophys. Res. Commun., 324: 133-139.

Camihort, G., D.C. Gomez, G. Luna, C. Ferese, S. Jurado and G. Moreno *et al*., 2005. Relationship between pituitary and adipose tissue after hypothalamic enervation in the female rat. A morphometric immunohistochemical study. Cells Tissues Organs, 179: 192-201.

Campbell, C.T., M. Prince, G.M. Landry, V. Kha and H.E. Kleiner, 2007. Pro-apoptotic effects of 1'-acetoxychavicol acetate in human breast carcinoma cells. Toxicol. Lett., 173: 151-160.

Cao, Z.F., Z.G. Chen, P. Guo, S.M. Zhang and L.X. Lian *et al*., 1993. Scavenging effects of ginger on superoxide anion and hydroxyl radical. Chung-Kuo Chung Yao Tsa Chih, 18: 750-751.

Chameau, P. and J.A. Van-Hooft, 2006. Serotonin 5-HT (3) receptors in the central nervous system. Cell Tissue Res., 326: 573-581.

Chang, C.C., 1964. A sensitive method for spectrofluorometric assay of catecholamines. Int. J. Neuropharmacol., 3: 643-649.

Chaparro-Huerta, V., M.C. Rivera-Cervantes, B.M. Torres-Mendoza and C. Beas-Zarate, 2002. Neuronal death and tumor necrosis factor-alpha response to glutamate- induced excitotoxicity in the cerebral cortex of neonatal rats. Neurosci. Lett., 333: 95-98.

Ciarlone, A.E., 1978. Further modification of a fluoremetric method for analyzing brain amines. Microchem. J., 23: 9-12.

Datta, A. and N.C. Sukul, 1987. Antifilarial effect of *Zingiber officinale* on dirofilaria immitis. J. Helminthol., 63: 268-270.

El-Abhar, H.S., L.N. Hammad and H.S. Gawad, 2008. Modulating effect of ginger extract on rats with ulcerative colitis. J. Ethnopharmacol., 118: 367-372.

Farmobi, E.O. and O.O. Onyema, 2006. Monosodium glutamate-induced oxidative damage and genotoxicity in the rat: Modulatory role of vitamin C, vitamin E and quercetin. Hum. Exp. Toxicol., 25: 251-259.

Fink, K.B. and M. Göthert, 2007. 5-HT receptor regulation of neurotransmitter release. Pharmacol. Rev., 59: 360-417.

Férézou, I., B. Cauli, E.L. Hill, J. Rossier, E. Hamel and B. Lambolez, 2002. 5-HT3 receptors mediate serotonergic fast synaptic excitation of neocortical vasoactive intestinal peptide cholecystokinin interneurons. J. Neurosci., 22: 7389-7397.

Ganong, W.F., 1990. Review of Medical Physiology. 19th Edn., Prentice-Hall International Inc., Connecticut, pp: 221-243.

Ghayur, M.N., A.H. Gilani, M.B. Afridi and P.J. Houghton, 2005. Cardiovascular effects of ginger aqueous extract and its phenolic constituents are mediated through multiple pathways. Vascul. Pharmacol., 43: 234-241.

Gill, S.S., R.W. Mueller, P.E. McGuire and O.M. Refined, 2000. Potential target sites in peripheral tissues for excitatory neurotransmission and excitotoxicity. Toxicol. Pathol., 28: 277-285.

Glowinski, J. and L.L. Iversen, 1966. Regional studies of catecholamines in the rat brain. I. The disposition of [3H] dopamine and [3H] dopa in various regions of the brain. J. Neurochem., 13: 655-669.

Govindarajan, V.S., 1982. Ginger-chemistry, technology and quality evaluation: Part 2. Crit. Rev. Food Sci. Nutr., 17: 189-258.

Grant, K.L. and R.B. Lutz, 2000. Ginger. Am. J. Health Syst. Pharm., 57: 945-947.

Greenway, F.L., Z. Liu, C.K. Martin, W. Kai-Yuan and J. Nofziger *et al*., 2006. Safety and efficacy of NT an herbal supplement in treating human obesity. Int. J. Obes. Lond., 30: 1737-1741.

Grzanna, R., L. Lindmark and C.G. Frondoza, 2005. Ginger-an herbal medicinal product with broad anti-inflammatory actions. J. Med. Food., 8: 125-132.

Gupta, Y.K. and M. Sharma, 2001. Reversal of pyrogallol-induced delay in gastric emptying in rats by ginger (*Zingiber officinale*). Methods Find Exp. Clin. Pharmacol., 23: 501-503.

Hasenohrl, R.U., C.H. Nichau, C.H. Frisch and M.A. De-Souza-Silva *et al*., 1996. Anxiolytic-like effect of combined extracts of *Zingiber officinale* and Ginkgo biloba in the elevated plus-maze. Pharmacol. Biochem. Behav., 53: 271-275.

Heal, D.J., A.T. Frankland, J. Gosden, L. Hutchins and M.R. Prow *et al*., 1992. A comparison on the effects of sibutramine hydrochloride, bupropion and methamphetamine on dopaminergic function evidence that dopamine is not pharmacological target for sibutramine. Psychopharmacology, 107: 303-309.

Heiman, M.L. and N. Ben-Jonathan, 1983. Increase in pituitary dopaminergic receptors after monosodium glutamate treatment. Am. J. Physiol., 245: E261-E265.

Hickok, J.T., J.A. Roscoe, G.R. Morrow and J.L. Ryan, 2007. A phase II/III randomized, placebo-controlled, double-blind clinical trial of ginger (*Zingiber officinale*) for nausea caused by chemotherapy for cancer: A currently accruing URCC CCOP cancer control study. Support Cancer Ther., 4: 247-250.

Hill, H.B., 1971. Principles of Medical Statistic. 9th Edn., Oxford University Press, USA.

Hoffman, T., 2007. Ginger: An ancient remedy and modern miracle drug. Hawaii. Med. J., 66: 326-327.

Huang, Q., H. Matsuda, K. Sakai, J. Yamahara and Y. Tamai, 1990. The effect of ginger on serotonin induced hypothermia and diarrhea. Yakugaku Zasshi, 110: 936-942.

Islam, M.S. and H. Choi, 2008. Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. J. Med. Food, 11: 152-159.

Johnston, C.A., E.J. Spinedi and A. Negro-Vilar, 1984. Effects of neonatal monosodium glutamate (MSG) treatment on the hormonal and central monoaminergic dynamics associated with acute ether stress in the male rat. Brain Res. Bull., 13: 643-649.

Kabuto, H., M. Nishizawa, M. Tada, C. Higashio, T. Shishibori and M. Kohno, 2005. Zingerone [4-(4-hydroxy-3-methoxyphenyl)- 2-butanone] prevents 6-hydroxydopamine-induced dopamine depression in mouse striatum and increases superoxide scavenging activity in serum. Neurochem. Res., 30: 325-332.

Kondoh, T. and K. Torii, 2008. MSG intake suppresses weight gain, fat deposition and plasma leptin levels in male sprague-dawley rats. Physiol. Behav., 95: 135-144.

Krishnakantha, T.P. and B.R. Lokesh, 1993. Scavenging of superoxide anions by spice principles. Indian J. Biochem. Biophys., 30: 133-134.

Kuo, P.C., A.G. Damu, C.Y. Cherng, J.F. Jeng and C.M. Teng, 2005. Isolation of a natural antioxidant, dehydrozingerone from *Zingiber officinale* and synthesis of its analogues for recognition of effective antioxidant and antityrosinase agents. Arch. Pharm. Res., 28: 518-528.

Levine, M.E., M.G. Gillis, S.Y. Koch, A.C. Voss, R.M. Stern and K.L. Koch, 2008. Protein and ginger for the treatment of chemotherapy-induced delayed nausea. J. Altern. Complement Med., 14: 545-551.

Lin, C.H., S.C. Kuo, L.J. Huang and P.W. Gean, 2006. Neuroprotective effect of N-acetylcysteine on neuronal apoptosis induced by a synthetic gingerdione compound: Involvement of ERK and p38 phosphorylation. J. Neurosci. Res., 84: 1485-1494.

Lombardi, G., G. Miglio, C. Dianzani, R. Mesturini and F. Varsaldi *et al*., 2004. Glutamate modulation of human lymphocyte growth *in vivo* studied. Biochem. Biophys. Res. Commun., 318: 496-502.

Lorden, J.F. and A. Caudle, 1986. Behavioral and endocrinological effects of single injections of monosodium glutamate in the mouse. Neurobehav. Toxicol. Teratol., 8: 509-519.

Mallick, H.N., 2007. Understanding safety of glutamate in food and brain. Ind. J. Physiol. Pharmacol., 51: 216-234.

Marles, R.J., J. Kaminski, J.T. Arnason, L. Pazos-Sanou and S. Heptinstall *et al*., 1992. A bioassay for inhibition of serotonin release from bovine platelets. J. Nat. Prod., 55: 1044-1056.

Martin, L.J., F.E. Sieber and R.J. Traystman, 2000. Apoptosis and necrosis occur in separate neuronal populations in hippocampus and cerebellum after ischemia and are associated with differential alterations in metabotropic glutamate receptor signaling pathways. J. Cereb. Blood Flow. Merab., 20: 153-167.

Moreno, G., M. Perelló, R.C. Gaillard and E. Spinedi, 2005. Orexin a stimulates hypothalamic-pituitary-adrenal (HPA) axis function, but not food intake, in the absence of full hypothalamic NPY-ergic activity. Endocrine, 26: 99-106.

Moreno, G., M. Perelló, G. Camihort, G. Luna, G. Console, R.C. Gaillard and E. Spinedi, 2006. Impact of transient correction of increased adrenocortical activity in hypothalamo-damaged, hyperadipose female rats. Int. J. Obes. (Lond), 30: 73-82.

Mowrey, D.B. and D.E. Clayson, 1982. Motion sickness, ginger and psychophysis. Lancent, 1: 655-657.

Nakagawa, T., K. Ukai, T. Ohyama, Y. Gomita and H. Okamura, 2000. Effects of chronic administration of sibutramine on body weight, food intake and motor activity in neonatally monosodium glutamate-treated obese female rats: Relationship of antiobesity effect with monoamines. Exp. Anim., 49: 239-249.

Oida, K., T. Nakai, T. Hayashi, S. Miyabo and R. Takeda, 1984. Plasma lipoproteins of monosodium glutamate-induced obese rats. Int. J. Obese., 8: 385-391.

Ojewole, J.A., 2006. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes (Zingiberaceae) in mice and rats. Phytother. Res., 20: 764-772.

Ortiz, G.G., O.K. Bitzer-Quintero, C. Beas-Zarate, S. Rodriguez-Reynoso and F. Larios-Arceo *et al*., 2006. Monosodium glutamate-induced damage in liver and kidney: A morphological and biochemical approach. Biomedecine Pharmacotherapy, 60: 86-91.

Ortuno-Sahagun, D., C. Beas-Zarate, G. Adame-Gonzalez and A.C. Feria-Velsco, 1997. Effect of L-glutamate on cholinergic neurotransmission in various brain regions and during the development of rats, when administered prenatally. Neurochem. Int., 31: 683-692.

Pavlovic, V., S. Cekic, D. Sokolovic and B. Djindjic, 2006. Modulatory effect of monosodium glutamate on rat thymocyte proliferationand apoptosis. Bratisl. Lek. Listy., 107: 185-191.

Pavlovic, V., D. Pavlovic, G. Kocic, D. Sokolovic and T. Jevtovic-Stoimenov *et al*., 2007. Effect of monosodium glutamate on oxidative stress and apoptosis in rat thymus. Mol. Cell, Biochem., 303: 161-166.

Riyazi, A., A. Hensel, K. Bauer, N. Geissler, S. Schaaf and E.J. Verspohl, 2007. The effect of the volatile oil from ginger rhizomes (*Zingiber officinale*), its fractions and isolated compounds on the 5-HT3 receptor complex and the serotoninergic system of the rat ileum. Planta Med., 73: 355-362.

Stricker-Krongrad, A., B. Beck, J.P. Nicolas and C. Burlet, 1992. Central effects of monosodium glutamate on feeding behavior in adult Long-Evans rats. Pharmacol. Biochem. Behav., 43: 881-886.

Suekawa, M., A. Ishige, K. Yuasa, K. Sudo, M. Aburada and E. Hosoya, 1984. Pharmacological studies on ginger. I. Pharmacological actions of pungent constituents, (6)-gingerol and (6)-shogaol. J. Pharmacobiodyn., 7: 836-848.

Sugita, S., K.Z. Shen and R.A. North, 1992. 5-hydroxytryptamine is a fast excitatory transmitter at 5-HT3 receptors in rat amygdale. Neuron, 8: 199-203.

Sun, Y.M., M.L. Ho, H.K. Hsu and M.T. Peng, 1993. The effects of neonatal monosodium glutamate treatment on sex-odor attractively and approach behavior in rats. Geoxig Yi. Xue. Ke. Xue. Za. Zhi., 9: 232-242.

Surh, Y.J., K.K. Park, K.S. Chun, L.J. Lee, E. Lee and S.S. Lee, 1999. Anti-tumor-promoting activities of selected pungent phenolic substances present in ginger. J. Environ. Pathol. Toxicol. Oncol., 18: 131-139.

Tanabe, M., Y.D. Chen, K. Saito and Y. Kano, 1993. Cholesterol biosynthesis inhibitory component from *Zingiber officinale* Roscoe. Chem. Pharm. Bull. (Tokyo), 41: 710-713.

Topic, B., E. Tani, K. Tsiakitzis, P.N. Kourounakis, E. Dere and R.U. Hasenöhrl *et al*., 2002. Enhanced maze performance and reduced oxidative stress by combined extracts of *Zingiber officinale* and ginkgo biloba in the aged rat. Neurobiol. Aging., 23: 135-143.

Ueki, S., M. Miyoshi, O. Shido, J. Hasegawa and T. Watanabe, 2008. Systemic administration of (6)-gingerol a pungent constituent of ginger, induces hypothermia in rat via an inhibitory effect on metabolic rat. Eur. J. Pharmacol., 584: 87-92.

Vishwakarma, S.L., S.C. Pal, V.S. Kasture and S.B. Kasture, 2002. Anxiolytic and antiemetic activity of *Zingiber officinale*. Phytother. Res., 16: 621-626.

Wallace, D.R. and R. Jr. Dawson, 1990. Effect of age and monosodium-L-glutamate (MSG) treatment on neurotransmitter content in brain regions from male Fischer-344 rats. Neurochem. Res., 15: 889-898.

Wortley, K.E., D.J. Heal and S.C. Stanford, 1999. Modulation noradrenaline concentration in rat frontal cortex and hypothalamus by alpha2-adrenoceptors. Br. J. Pharmacol., 128: 659-666.

York, D.A., S. Thomas, F.L. Greenway, Z, Liu and J.C. Rood, 2007. Effect of an herbal extract Number Ten (NT) on body weight in rats. Chin. Med., 14: 2-10.

Yoshida, T., H. Nishioka, Y. Nakamura and M. Konodo, 1984. Reduced norepinephrine turnover in mice with monosodium glutamate-induced obesity. Metabolism, 33: 1060-1063.