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Neuroprotective Effect of *Garcinia Mangostana* on Streptozotocin Induced Sporadic Type Alzheimer's Disease in Mice

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ABSTRACT:

Objectives: The main objective of the study is to determine the neuroprotective potential of ethonolic extract of *Garcinia mangostana* (EEGM) in mouse against Intracerebroventricular-Streptozotocin (ICV –STZ) induced sporadic type Alzheimer's disease.

Methods: Neurotoxicity was induced by ICV injection of STZ (0.5 mg/kg/b.w) as a first dose then the second dose after the 48 hours and the animals were pre-treated with ethanolic extract of *Garcinia mangostana* for 28 days. To assess the behavioral parameters learning and memory, open field and Y-maze were employed. Acetylcholinesterase, antioxidant enzymes (superoxide dismutase, glutathione peroxidise, reduced glutathione and catalase) were estimated in brain tissue. **Results:** Pre-treatment with EEGM (200 and 400 mg/kg/b.w) exhibited a dose dependent reduction of AChE levels and increased habituation memory and percentage alteration which are indicative of the enhanced cognitive function. The extract showed significant increase in the antioxidant parameter.

Conclusion: The study results suggested that the neuroprotective potentiality of EEGM against ICV STZ induced neurotoxicity. The extract of EEGM proved to have a potential therapeutic action in preventing or decreasing the progression of sporadic Alzheimer's disease due to aging and oxidative stress.

1. INTRODUCTION

Dementia is a general term for a decline in mental ability severe enough to interfere with daily life. It may result from aging, brain injury, Infections, vitamin or hormonal imbalance or consumption of drugs or alcohol. Dementia is not a disease in itself, but rather a group of symptoms representing specific brain structural diseases and several system degenerations.

There are 70-80 different types of dementia. The most common types are associated with Alzheimer's disease (AD) and old age. Alzheimer's disease is the most common cause of dementia and memory impairment in the elderly people. AD is classified into two forms namely familial type and sporadic (SAD). The SAD is characterized by cognitive deficits and extensive neuronal loss in the central nervous system (Michon et al., 2009; Reed et al., 2009). Aging is the main risk factor for late-onset SAD and it is a multifactorial disease containing both genetic and epigenetic factors. (Zawia et al., 2009).

Earlier studies indicate that disturbances of several aspects of cellular metabolism appear pathologically important in SAD. Among these, increased brain insulin resistance (Salkovic et al., 2008) , decreased glucose utilization and energy metabolism are observed in the

early stages of the disease (Torre et al., 2008), consequently energy deficit, oxidative stress (Droge et al., 2008) and inflammation (Monte et al., 2005) in neuronal tissue are the further cause of neurodegeneration in SAD.

ICV injection of STZ in mice was reported to impair brain biochemical reactions, cerebral glucose and energy metabolism, cholinergic transmission, and increases generation of free radicals, ultimately leading to cognitive deficits (Lannert et al., 1998; Ishrat et al., 2009a; Ishrat et al., 2009b). Collectively, these effects are similar to sporadic dementia of Alzheimer's type in humans (Hoyer et al., 1991). According to the earlier reports, the ICV injection of STZ causes progressive deficits in learning and memory (Lannert et al., 1998; Awasthi et al., 2010) and cause oxidative stress in animals (Sharma et al., 2000). In addition, the activity of acetyl cholinesterase (AChE) was also increased in the said model (Hellwey et al., 1992).

Xanthones are restricted plant polyphenols which have strong antioxidative potential, might affect the amyloidogenic process and thus exert neuroprotective activity. Alpha-Mangostin, a novel polyphenolic xanthone derived from the pericarp, bark and dried sap of mangostin (Garcinia mangostana Linn).

In age old days it was used by people in tropical countries as a traditional medicine to cure abdominal pain, diarrhoea, dysentery, infected wound suppuration, chronic ulcer and exhibited a broad range of bioactivities (Pedraza et al., 2008). Several *in vitro* and *In vivo* studies had revealed the antioxidant (Weecarangsan et al., 2006), anti-inflammatory (Chen et al., 2008), anti-cancerogenic properties (Matsumoto et al., 2003), anticholinesterase and neuroprotective (Tangponga et al., 2011) properties of Alpha-Mangostin.

An in vitro study of Alpha-Mangostin on rat cerebral neurons has proven its efficacy in inhibiting the formation of amyloid beta fibrils and protected the neurons against amyloid beta oligomers-induced toxicity (Wang et al., 2012).

The present study is aimed at evaluating the neuroprotective potentiality of ethanolic extracts obtained from the fruits of *Garcinia mangostana* in ICV streptozotocin-induced mouse model for assessing its efficacy in sporadic type Alzheimer's disease.

2. METHODOLOGY

2.1 Drugs and chemicals

Streptozotocin; DTNB (5,5'-dithiobis(2-nitron benzoic acid), Eserine Acetylthiocholine iodide, Pyrogallol and Dexamethasone were purchased from Sigma Aldrich, USA. Bovine serum albumin, Sodium carbonate, Sodium hydroxide, Copper sulphate, Sodium Potassium Tartarate, Folin Ciocalteau's reagent; Ninhydrin, Tris-HClbuffer; Hydrochloricacid, Tris-EDTA buffer; DETPA, Ammonium molybdate, Hydrogen peroxide; Sodium dihydrogen phosphate, Disodium hydrogen phosphate; Sodium azide, Reduced glutathione; TCA and sodium citrate were purchased from S.D Fine Chemicals, India

2.2 Plant material and Extraction

The Unriped fruits of *Garcinia mangostana* were collected from the forests of chittoor district of Andhra pradesh during the month of April. The fruits were authenticated by DR K. Madhava Chetty, Assistant Professor, Department of Botany, Sri Venkateshwara University, Tirupati. A vocher specimen wide no: UT-GM-006-10 .The fruit of *Garcinia mangostana* were cleaned to remove any residual compost. The hulls were separated and then were dried. All dried hulls were ground to powder and placed in 70°C distilled water at the ratio of 1: 4. The mixtures were boiled 4 times until no content of tannin was found. It was confirmed by testing with 2% gelatin solution. The macerate filtrate was dried at room temperature. The dry powder was macerated at room temperature for 7 days with 50% ethanol. The hydro-alcoholic extracts were filtered and concentrated using rotary vacuum evaporator. The concentrated extracts were dried at room temperature and stored in a well closed container avoiding microbial contamination.

2.3 Experimental animals

Male Swiss albino mice, weighing 20-35g, at the age 3-4 weeks were used in the study. They were maintained on standard laboratory pellet chow diet, Provimi limited (India), provided water *ad libitum* and were kept under standard conditions at 23-25 ^{0}c, 35 to 60% humidity, 12hr light /dark cycle. The mice were acclimatized to the laboratory conditions a week prior to experiment. The experimental protocol was duly approved by institutional animal ethics committee (IAEC) wide no: **I/IAEC/LCP/002/2012/SM/24.** The animal experimentation was carried out under CPCSEA registration.

2.4 Acute toxicological studies

The procedure was followed by using OECD guidelines 423 annexure D (Acute Toxic Class Method). The acute toxic class method is a step wise procedure with three animals of single sex per step. The starting dose level of EEGM was 2000 mg/kg b. w, p.o as most of the crude extracts possess LD_{50} value more than 200 mg/kg/b.w, p.o. Drug was administered to overnight fasted mice. Food was withheld for a further 3-4 hours after administration of EEGM and observed for signs for toxicity.

2.5 Induction of neurotoxicity and grouping

Neurotoxicity is induced by ICV injection of STZ (0.5 mg/kg) by identifying the bregma point in skull; In brief, bregma point was identified according to Laursen& Belknap (Laursen et al., 1986), by rubbing the point of

needle over the skull (approximately 1–3 mm rostral to the line drawn through anterior base of ears), then at 450 angle the needle was inserted 2 mm lateral to midline and STZ was injected.

Animals were divided into four groups containing in each group six animals. Group I was treated with phosphate buffered saline alone; Group II injected with two doses of STZ (0.5 mg/kg) ICV injection bilaterally. The second dose was administered after 48 h of first dose. Group III and Group IV are pre-treated with ethanolic extract of *Garcinia mangostana* (EEGM) orally for 21 days; on 21st day Group III and Group IV are injected with STZ ICV and the second dose was administered after 48 h of first dose and the treatment with EEGM was continued for 28 days. STZ was dissolved in phosphate buffered saline.

2.6 Behavioural studies

2.6.1 Video tracking in Y Maze

Y-maze task was used to measure the spatial working memory in rats. The maze is made of perspectives. Mice tend to explore the maze systematically, entering each arm inturn (Reddy et al., 1997).

2.6.2 Open field habituation

The exploratory behaviour of the mice was evaluated by using the open field habituation task method(Maria et al., 2005).

2.7 IN-VIVO STUDIES

2.7.1 Acetyl cholinesterase

The whole brain acetylcholinesterase activity was determined using the method of Ellman (Ellman et al., 1961), The presence of brain cholinesterase was measured using a spectrophotometer at 420nm (UV- 1800, Shimadzu, Japan).

2.7.2 Reduced Glutathione (GSH)

GSH levels in the brain were determined using the method of Beutler (Beutler et al., 1963). The levels of glutathione were measured using spectrophotometrically at 412 nm (UV- 1800, Shimadzu, Japan).

2.7.3 Antioxidant Enzyme Activity

2.7.3.1 Superoxide dismutase.

Superoxide dismutase activity was determined by the pyrogallol oxidation method (Marklund et al., 1974).The reaction is initiated by adding pyrogallol to the sample and the change in optical density was recorded at 420 nm using spectrophotometer (UV- 1800, Shimadzu, Japan).

2.7.3.2 Glutathione peroxidase.

Glutathione peroxidase activity was assayed by using Lawrence and Burk method (Lawrence et al., 1976). The decrease in NADPH absorbance measured at 340nm during the oxidation of NADPH to NADP+ is an indicative of glutathione peroxidase activity, since glutathione peroxidase is the rate limiting factor of the coupled reactions

2.7.3.3 Catalase

Catalase activity was assayed according to Goth method (Goth et al., 1991). One unit of the enzyme was defined as millimoles of H_2O_2 degraded/min/mg by protein used.

3. STATISTICAL ANALYSIS:

The data values are presented as Mean ±S.E.M. The significance of difference among the groups were assessed by using one way analysis of variance (ANOVA) followed by Tukey's test using Graph pad prism version 5.0 software and $p \leq 0.05$ was considered as significant.

4. RESULTS

4.1 Acute toxicity report

The extract was administered orally to the mice then the body weight of the mice before and after administration of EEGM was recorded. The changes in fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system and motor activity and behaviour pattern were observed and also sign of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma were monitored for 14 days of treatment. The onset of toxicity and signs of toxicity also observed. The extract LD50 was found to be non-toxic, and the dose 2000 mg/kg and above can categorised as "unclassified" for the GHS of OECD 423.

4.2 Behaviour Parameters:

4.2.1 Effect of EEGM on Y- Maze

Effect of EEGM on percentage spontaneous alteration in spatial learning and memory were tabulated in Table: 1. Administration of STZ significantly ($P< 0.001$) decreased the percentage spontaneous alteration in negative group when compared to that of vehicle treated group. The group treated with 200 mg/kg and 400 mg/kg EEGM increased the percentage spontaneous alteration in mice and showed the significance of ($P< 0.01$and $P<0.001$) respectively.

4.2.2 Effect on Open field habituation

The open field results were also tabulated in the Table: 1, the exploratory behaviour i.e., the number of line crossings and head dippings in mice decreased in STZ treated group ($P< 0.001$) in comparison with control group. The number of line crossings and head dippings increased significantly ($P< 0.05$ and $P<0.01$) in both 200 mg/kg and 400 mg/kg/b.w of EEGM treated groups respectively and indicating the open field habitutation memory enhancement.

4.3 Biochemical Parameters

4.3.1 Effect of EEGM on AChE activity

Effect of EEGM on AChE was tabulated in Table: 2. Administration of STZ significantly (P< 0.001) increased the AChE activity in mice when compared to the vehicle treated group. Treatment of EEGM significantly (P<0.05 and P< 0.001) attenuated the raise in enzyme level in 200 mg/kg and 400 mg/kg treated mice groups respectively.

4.3.2 Effect of EEGM on Superoxide dismutase

Administration of STZ significantly (P< 0.001) decreased the activity of SOD when compared to the vehicle treated control group. Treatment with EEGM 200 mg/kg and 400 mg/kg doses showed a significant increase (P< 0.01 and P< 0.001) in activity of SOD respectively compared to negative control group. The results were shown in Table: 2.

4.3.3 Effect of EEGM on Catalase:

Administration of STZ significantly (P<0.001) decreased the activity of catalase in mice when compared to the vehicle treated group. The animals treated with EEGM 200 mg/kg and 400 mg/kg doses showed a significant increase in (P<0.05, and P<0.001) the catalase levels respectively in comparision to only STZ treated group. There was an evidence of dose dependent increase in Catalase on administration of EEGM with P< 0.05. The results were also tabulated in Table: 2.

4.3.4 Effect of EEGM on Glutathione peroxidase (GPx):

Administration of STZ significantly (P< 0.001) decreased the activity of GPx when compared to the vehicle treated group in mice. The two groups of animals treated with EEGM 200 mg/kg and 400 mg/kg doses showed a significant increase (P< 0.05 and P< 0.001) in activity of glutathione peroxidase respectively compared to STZ only treated group. The results were shown in Table: 2.

4.3.5 Effect of EEGM on Gluthathione:

Administration of STZ significantly (P<0.001) decreased the activity of glutathione in mice when compared to the vehicle treated group. The animals treated with EEGM 200 mg/kg and 400 mg/kg doses showed a significant increase (P<0.01, P<0.001) respectively in activity of glutathione compared to only STZ treated group. The results were also tabulated in Table:2.

Table 1: Effect Of EEGM On Behaviour Parameters

Groups	Y-Maze	Exploratory Behaviour	
		Line Crossing	**Head dippings**
Group I (I.C.V PBS)	44.61 ± 1.931	137.0 ± 10.43	20.00 ±2.955
Group II (I.C.V STZ 0.5mg/kg)	19.39 ± 1.300 [a]	80.00 ± 4.344[a]	6.167± 0.9458[a]
Group III (I.C.V STZ+EEGM 200mg/kg)	32.12 ± 1.722 [b]	117.5± 9.465[e]	15.17± 1.905[e]

Values are expressed as mean ± SEM of 6 animals. Superscript letters represents the statistical significance done by ANOVA, followed by Tukey's multiple comparison tests.

[a] P< 0.001, indicates comparison of Group II with Group I. [b]P< 0.01, indicates comparison of Group III and IV with Group II. [c]P< 0.001, indicates comparison of Group III and IV with Group II. [d]P<0.01, indicates dose dependant significance on comparing Group III&IV. [e] P<0.05, indicates comparison of Group III and IV with Group II respectively. [f] P< 0.01, indicates comparison of Group III and IV with Group II respectively.

Table 2: Effect of EEGM on ACHE and Anti oxidant Enzymes

Parameters	Group I (I.C.V PBS)	Group II (I.C.V STZ 0.5mg/kg)	Group III (I.C.V STZ+EEGM 200mg/kg)	Group IV (I.C.V STZ +EEGM 400mg/kg)
Acetyl cholinesterase	13.84 ± 1.83	69.61 ± 5.42[a]	53.20 ± 2.50[b]	33.20 ± 3.29[c, d]
Superoxide dismutase	18.44 ± 0.89	5.28 ± 0.96[a]	10.74 ± 0.98[e]	15.94 ± 0.61[c, d]
Catalase	1.298 ± 0.081	0.64 ± 0.046 [a]	0.92 ± 0.04[b]	1.18 ± 0.042 [c, f]

Glutathione peroxidase	28.85 ± 1.09	14.85 ± 1.27[a]	20.23 ± 1.28[b]	25.38 ± 0.76[c, f]
Glutathione	63.90 ± 3.89	10.15 ± 1.33[a]	29.41 ± 1.92[d]	42.66 ± 4.85[c]

Values are expressed as mean ± SEM of 6 animals. Superscript letters represents the statistical significance done by ANOVA, followed by Tukey's multiple comparison tests.

[a] P< 0.001, indicates comparison of Group II with Group I. [b]P< 0.05, indicates comparison of Group III and IV with Group II. [c]P< 0.001, indicates comparison of Group III and IV with Group II. [d]P<0.01, indicates dose dependant significance on comparing Group III&IV. [e] P<0.01, indicates comparison of Group III and IV with Group II respectively. [f] P< 0.05, indicates comparison of Group III and IV with Group II respectively.

5. DISCUSSION:

The present study was mainly emphasized on pre-treatment effect of EEGM on cognitive deficits, cholinergic dysfunction and oxidative stress in intracerebroventricular-streptozotocin (ICV-STZ) induced model of sporadic dementia (SAD) type Alzheimer's disease in mice. The ICV-STZ rodent model is a well established animal model for the study of sporadic dementia of Alzheimer type (Hoyer et al., 1991; Agarwal et al., 2009).

Aging is the main risk factor for late-onset SAD (Placancia et al., 2009). Numerous changes are accentuated by stress particularly the functional imbalances of regulative systems, such as reduced energy production, an increased energy turnover, lowered insulin action and increased cortisol action (Cizza et al., 1994).

Intracerebroventricular injection of streptozotocin, causes prolonged impairment of brain glucose utilization which could explain the impairment of spatial memory induced by ICV-STZ injection in rats (Prickaerts et al., 1999; Weinstock et al., 2004). Previous experiments also reported that there is a direct damage to the septo-hippocampal system on ICV injection of STZ (Blokland et al., 1993). Oxidative stress that has developed due to ICV injection of STZ (Feillet et al., 1999) known to cause damage to the myelin of neurons which known to be responsible for spatial memory deficits in animal models (Shoham et al., 2003).

In this present study, the Ethanolic Extract of Garcinia mangostana was selected as it contains xanthones, a polyphenolic compounds (Govindachari et al., 1971; Peres et al., 2000; Sultanbawa et al., 1980) such as alpha, beta and gamma mangosteens known to have significant and potent antioxidant, anti-inflammatory and neuroprotective activities.

The results revealed that the ICV-STZ administered group II mice has shown a significant reduction in spatial learning and memory recognition in comparison with vehicle treated group. It was confirmed by Y-maze test which mainly emphasize upon reduction in percentage of spontaneous alteration in mice. The Pre-treated animals with (200 and 400 mg/kg, b.w) EEGM in group III and IV have shown a significant rise in Y-maze test, when compare to that of treatment group II.

ICV injection of STZ in the present study also led to the development of habituation memory impairment which was assessed by open field test. Habituation memory is related to the measurement of exploratory behaviour (crossings and head dips) which was reduced in group II. However, the pre-treatment with EEGM in group III and IV has increased the number of head dipping and line crossings of mice.

Free radical-induced damage to macromolecules (lipid, sugar, protein and nucleic acids) plays an important factor in the acceleration of aging and age-related neurodegenerative disorders such as AD (Liu et al., 2001; Wickens et al., 2001). The brain is very susceptible to the damage caused by oxidative stress, due to its rapid oxidative metabolic activity, high polyunsaturated fatty acid content, relatively low antioxidant capacity, and inadequate neuronal cell repair activity (Halliwell et al., 2001). ICV-STZ administration in mice impairs brain biochemical reactions (Plaschke et al., 1993) and increases the generation of free radicals and also significantly alter the levels of biomarkers for oxidative damage; thiobarbituric acid, glutathione, glutathione peroxidase, glutathione reductase within a 2-3 weeks after ICV -STZ administration (Ishrat et al., 2009b). The study results revealed that the ICV injection of STZ in group II resulted in oxidative stress which was characterized by significant reduction in antioxidant enzymes such as catalase, glutathione peroxidase, superoxide dismutase , reduced glutathione and reduced glutathione levels in comparison to group I.

Xanthones, a class of polyphenolic compounds, are biologically active antioxidant phytonutrients that neutralizes the free radicals and promote healthy cardiovascular, gastrointestinal and nervous systems functions (Jiang et al., 2003; Kondo et al., 2009; Marquez et al 2009). The major xanthone in Garcinia mangostana fruit rind is α-mangostin, which possesses medicinal benefits and potential free radical and antioxidant activity properties. Pre-treated animals with EEGM In group III and IV has exhibited significant antioxidant activity against ICV injection of STZ as an evident from the rise in reduced glutathione levels (GSH) and antioxidant enzyme such as catalase, superoxide dismutase, glutathione peroxidase in comparison to group II received an ICV injection of STZ.

ICV injection of STZ is also known to induce an increase in acetylcholinesterase activity which further deprives available ACH involved in the memory functions. In the present study ICV injection of STZ found to increase acetylcholinesterase activity in group II injected only with ICV STZ. In this study, pre-treatment with EEGM in group III and IV has showed a significant inhibition of acetyl cholinesterase activity, elevated due to ICV injection of STZ.

6. SUMMARY AND CONCLUSION:

The study revealed that the neuoroprotective potential of EEGM against oxidative stress and cognitive deficits due to ICV injection of STZ. Hence, it can be concluded that the EEGM contains compounds of antioxidant and anticholinesterase potential. The cognitive deficits and oxidative stress in sporadic Alzheimer's are need to be further investigation with respect to their molecular mechanisms involved in the neuroprotective activity of Garcinia mangostana.

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