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ASPARTAME CONSUMPTION IN DIABETES MALE ALBINO RATS - COMPLICATIONS IN BRAIN ANTIOXIDANT SYSTEM

Ediga Madhu Goud, Annapureddy Suvarna and Salikineedy Kishore *

Division of Toxicology, Department of Zoology, Sri Venkateswara University, Tirupati - 517502, Andhra Pradesh, India.

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Correspondence to Author:
Dr. S. Kishore

Professor,
Division of Toxicology,
Department of Zoology,
Sri Venkateswara University,
Tirupati - 517502, Andhra Pradesh, India.

E-mail: kishorecsb@gmail.com

ABSTRACT: The present study investigated the effect of intake of aspartame in diabetic rats, a widely used artificial sweetener (aspartame), on antioxidant defence status in the rat brain. Adult male Wistar rats weighed 180 ± 20 gm were randomly divided into 4 groups as follows: The first group was control; the second group was given aspartame (ASP) at a dose of 50 mg/kg body weight; the third group was Diabetes (D) (Streptozotocin (STZ) 45 mg/kg body weight); and fourth group was Diabetes rats (STZ 45 mg/kg body weight) administered with ASP (D+ASP) (50 mg/kg body weight). Induction of Diabetes (STZ) through intraperitoneal injection at a single dose. ASP is administered with gavage for up to 30 days. Superoxide dismutase, catalase and glutathione reductase are significantly reduced. In contrast, in lipid peroxidation, a significant increase was observed in the various brain regions of the experimental group rats compared with the control group rats. The results indicate that consumption of aspartame leads to an imbalance in the normal and diabetic rats' antioxidant/pro-oxidant status in the brain through the mechanism of the glutathione-dependent system. These effects lead to non-communicable diseases in the brain.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia and defects of insulin secretion [1]. According to International Diabetes Federation (IDF) and World Health Organization (WHO), approximately 463 million adults are living with diabetes. The total number is predicted to rise to 578 million by 2030 and 700 million by 2045 [2]. Diabetes is a stress-related disorder that shows increased free radical formation and oxidative stress, weakening antioxidant defences, and impaired antioxidant enzyme activity [3].

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Due to a lack of antioxidant defences, diabetes indices such as hyperglycemia, glucose variability, and hypoglycemia may contribute to oxidative stress development [4]. In addition, in several neurological disorders (Parkinson's, Alzheimer's, and Schizophrenia diseases), reactive oxygen species are majorly involved [5]. In this connection, Artificial sweeteners are recognized as sugar substitutes for managing diabetes. Patients consume protein and fiber-rich nutrient supplements containing various artificial sweeteners to limit their sugar levels and weight loss.

The US FDA has approved six artificial sweeteners for human usage aspartame, saccharine, neotame, acesulfame-K, stevia, and sucralose [6]. Additionally, the manufacturers of beverages, dairy products, and pharmaceuticals have been utilizing these artificial sweeteners in their products. Consequently, people

are consuming these artificial sweeteners somehow through the above products indirectly [7]. Further, people are inspired to utilize artificial sweeteners in enormous quantities for weight loss management. There is substantial evidence that artificial sweeteners can be considered the primary reason for developing diabetes [8]. Moreover, artificial sweetener produces a high sweetness that negatively affects insulin production from the pancreas, which is confused for glucose sweetness [9]. Besides its benefits, side effects are more in animal studies report that non-nutritional sweeteners lead to oxidative stress [10].

Aspartame is present in more than 6000 food products in everyday usage by American people and worldwide. However, it remains the most controversial food product [11]. US Food and Drug Administration (FDA) approved aspartame usage in limited quantity in 1981; in 1996 (US FDA), 2006), aspartame was approved as a general sweetener and set 50 mg as an acceptable daily intake (ADI). However, the World Health Organization (2004) and Europe food regulatory authorities consider 40 mg as ADI [12].

Several food products use aspartame as a sweetener, like breakfast cereals, soft drinks, chewable multivitamins, chewing gums, beverages, cakes, yogurts, and pharmaceuticals [13]. Aspartame metabolites consist of phenylalanine (50%), aspartic acid (40%), and methanol (10%); among these, methanol is toxic and causes severe toxicity to the brain [14]. The amino acid Phenylalanine is essential for synthesising monoamine in the brain and is present in nearly all food products containing proteins [15]. In addition, more amounts of phenylalanine in the circulatory system may cause brain damage [16]. Aspartic acid is an excitatory amino acid in the brain, and the blood-brain barrier controls it at all levels. Therefore, these amino acid levels increase in the brain after aspartame consumption and disturb the brain. Another metabolite of aspartame, methanol is metabolized into formaldehyde and formate and in turn, these form into superoxide anion and hydrogen peroxide that causes systemic toxicity [12]. Some reports established aspartame intake affects on the neurological system resulting in headache, seizures, depression, cancer, behavioural changes, and alterations in the catecholamines [17].

Previous studies on aspartame show the increased impact of free radicals in the brain [18]. The brain is susceptible to oxidative stress [19] and the Aspartame metabolite methanol may cause severe oxidative stress in the brain [20]. Due to these antioxidant enzymes, activity imbalances in the brain cause severe neuronal health effects.

ASP is well known for its neurobehavioral disorders and carcinogen properties, but interestingly, aspartame is still used in many diet foods, including those used by diabetic people, obese, and others. Thus, we would like to explore this because there are few detailed studies on oxidative stress caused by using ASP in people with diabetes. In the present investigation, we aimed to examine antioxidant enzyme alterations in the ASP-administered diabetes rats' brain. However, the literature about this study is sparse.

MATERIALS AND METHODS:

Procurement and Maintenance of Animals: Adult male Wistar albino rats, with an average body weight of 180 ± 20gm, were purchased from an authorized vendor (Sri Venkateswara Enterprises, Bengaluru, India) and used for experimental analyses. Rats were randomly selected and housed in polycarbonate cages lined with sterilized paddy husk and provided with filtered tap water and standard rat food *ad libitum*. Rats were acclimatized (temperature 25±2°C, 12h dark/light cycle and 50 - 60% relative humidity) for 2 weeks before being used in the experiment to adapt to the new environment. All experiments on animals were performed in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Government of India. The protocol was approved by the Institutional Animal Ethics Committee (Regd. No. 438/01/a/CPCSEA/dt.17-07-2001) and has (Resolution no. 10/(i)/a/CPCSEA/IAEC/SVU/ZOOL/SK/dt.08-07-2012). During the research process, maximum precautions are taken.

Chemicals: Aspartame (purity 98%) was purchased from (Himedia Laboratories Pvt. Ltd. Mumbai, India) and Streptozotocin (purity 98%) was purchased from (Sisco Research Laboratories Pvt. Ltd. Taloja, Maharashtra, India) and all other chemicals were of analytical grade.

Experimental Design: A total of 24 rats was characterized into 4 groups, 6 rats were placed in each group and treated as follows:

Group I: Control (C): Animals in this group were orally1 ml saline (0.9%) given daily.

Group II: Aspartame (ASP) administrated rats: Animals in this group were orally administered a freshly prepared ASP solution (50 mg/kg body weight) diluted in sterile saline daily via oral gavage for 30 days.

Group III: Diabetes (D) induced rats: Animals in this group were treated with a single intraperitoneal dose of Streptozotocin (STZ) (45 mg/kg body weight).

Group IV: Diabetes (D) rats administered with ASP (D+ASP): Animals in this group were treated with STZ and administered with ASP in the same manner as groups II and III.

Induce diabetes by using Streptozotocin (STZ): Adult male albino rats were fasted overnight and rendered diabetic through a single intraperitoneal (i.p.) dose of a freshly prepared STZ solution (45 mg/kg body weight) dissolved in 0.1 M citrate buffer (pH 4.5). To conquer drug-induced hypoglycemia, rats were given a 10% glucose solution overnight. On the third day after STZ administration, diabetes was confirmed by polydipsia, polyuria, and weight loss. Only rats with blood glucose levels over 250 mg/dL based on a cut-made tail region with Accuchek Glucometer were considered diabetes.

Administration of Aspartame (ASP): ASP administration was started on the third day after the STZ injection, which was considered the first day. ASP was orally administered as 0.9% sterile saline by the oral gavage at a dose of 50 mg/kg body weight for 30 consecutive days. The general appearance of the animal and signs of toxicity such as behaviour (irritability, alertness, vomiting, restlessness and fearfulness), neurological (gait, spontaneous activity, bleeding orifices and response to touch/pain) and autonomic (micturition and defecation) were continuously monitored during the experiment.

Necropsy: After the completion of the experimental period (30 days), the rats were fasted overnight, weighed, and sacrificed by cervical dislocation. The regions of the brain, such as the hippocampus (HP), cerebral cortex (CC), cerebellum (CB), and ponsmedulla (PM) were promptly dissected out, washed with ice-cold saline, weighed to the nearest milligram, and then excised at 4°C. In addition, the tissues were immersed in liquid nitrogen and stored at -80°C for further biochemical analysis.

Analytical Procedures: The activity of SOD was determined by Misra and Fridovich (1972) [21] using the UV- spectrophotometer at 480 nm for 4 min. The activity was expressed as an amount of enzyme that inhibits the oxidation of epinephrine by 50%, equal to 1 unit per milligram of protein. The activity of CAT was estimated by the modified method of Aebi (1984) [22]. The absorbance of the sample was measured at 240 nm for 1 min in a UV spectrophotometer. GR activity is assayed by Carlberg and Mannervik (1985) [23] absorbance at 340 nm for 3 min UV spectrophotometer. Lipid Peroxidation extent was assayed as the concentration of Thiobarbituric acid reactive product MDA by the method of Ohkawa *et al.*, (1979) [24] at the absorbance of 532 nm against the reagent blank in a spectrophotometer (Hitachi U-2000). Tissue protein was estimated by the method of Lowry *et al.*, (1951) [25] measured at 600 nm in a UV spectrophotometer. Bovine serum albumin was used as a standard. All the enzyme activities are expressed per mg protein.

Statistical Analysis: The experiment was performed, and data were expressed as mean ± SD. One-way analysis of variance (ANOVA) followed by Scheffe, Duncan and Dunnet's multiple range test was used to evaluate the results, and $p < 0.05$ was considered significant. Statistical analysis was performed using the SPSS v20.0 (SPSS, Chicago, 1L, USA) statistical program.

RESULTS:

Superoxide Dismutase (SOD): The results revealed that the SOD activity in the brain regions (HP, CC, CB and PM) of experimental and control group rats **Fig. 1**. Aspartame administered causes a significant decline in the SOD activity in the brain regions (HP, CC, CB and PM) of ASP and Diabetes groups compared with the control group rats. Interestingly Aspartame administered to

diabetes induced (D+ASP) group rats demonstrated a significantly declined ($p < 0.05$) activity of SOD in the brain regions (HP, CC, CB and PM) compared with C, ASP and D groups. Aspartame administered to diabetes induced rats showed a more harmful effect on the brain regions than the remaining groups, as shown in **Table 1**.

TABLE 1: EFFECT OF ASPARTAME ON SUPEROXIDE DISMUTASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Groups	HP	CC	CB	PM
C	6.656 ± 0.655	7.258 ± 0.647	6.968 ± 0.693	6.408 ± 0.738
ASP	5.142 ± 0.502*	6.17 ± 0.497*	5.73 ± 0.524*	4.979 ± 0.544*
D	3.786 ± 0.491 $^{\Psi}$	4.884 ± 0.418 $^{\Psi}$	4.456 ± 0.465 $^{\Psi}$	3.709 ± 0.562 $^{\Psi}$
D+ASP	2.611 ± 0.58$^{\#}$	3.378 ± 0.578$^{\#}$	3.205 ± 0.427$^{\#}$	2.612 ± 0.557$^{\#}$

HP: Hippocampus, CC: Cerebral cortex, CB: Cerebellum, PM: Ponsmedulla. C: Control, ASP: Aspartame, D: Diabetes, D+ASP: Diabetes + Aspartame. Values are Mean ± SEM of n= 6 rats. Values are significantly different from control group * Ψ # $p < 0.05$.

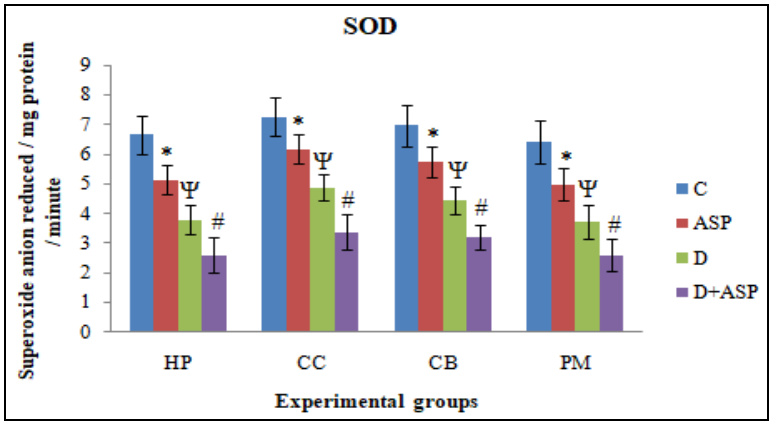

FIG. 1: EFFECT OF ASPARTAME ON SUPEROXIDE DISMUTASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Catalase (CAT): The results obtained in the present study clearly demonstrated the activity of CAT in the brain regions (HP, CC, CB and PM) of control and experimental group rats **Fig. 2**. On the contrary, the results on the ASP and in Diabetes group showed a significant decline ($p < 0.05$) in CAT activity in selected brain regions, compared with the control group. However, the simultaneous ASP-administered Diabetes group showed a significant decline ($p < 0.05$) in the CAT activity in HP, CC, CB and PM of brain regions compared with control group rats. The values are reported in **Table 2**.

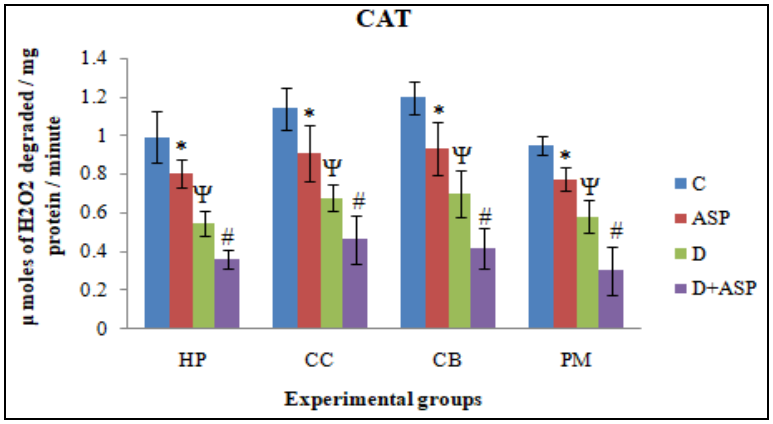

FIG. 2: EFFECT OF ASPARTAME ON CATALASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

TABLE 2: EFFECT OF ASPARTAME ON CATALASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Groups	HP	CC	CB	PM
C	0.992 ± 0.132	1.14 ± 0.108	1.197 ± 0.084	0.949 ± 0.046
ASP	0.802 ± 0.073*	0.909 ± 0.146*	0.933 ± 0.14*	0.775 ± 0.061*
D	0.548± 0.066 $^{\Psi}$	0.679 ± 0.071 $^{\Psi}$	0.7 ± 0.124 $^{\Psi}$	0.581 ± 0.086 $^{\Psi}$
D+ASP	0.361 ± 0.048$^{\#}$	0.463 ± 0.124$^{\#}$	0.417 ± 0.102$^{\#}$	0.303 ± 0.124$^{\#}$

HP: Hippocampus, CC: Cerebral cortex, CB: Cerebellum, PM: Ponsmedulla. C: Control, ASP: Aspartame, D: Diabetes, D+ASP: Diabetes + Aspartame. Values are Mean ± SEM of n= 6 rats. Values are significantly different from control group * Ψ # $p < 0.05$.

Glutathione Reductase (GR): In the present study, it was noticed that GR activity in the brain regions (HP, CC, CB, and PM) of control and experimental groups rats **Fig. 3** it was observed that the ASP and Diabetes group showed a significant decreased ($p < 0.05$) in the GR activity in selected brain regions. However, simultaneous ASP administered to diabetes group rats (D+ASP) showed significantly reduced ($p < 0.05$) GR activity in HP, CC, CB and PM of brain regions when compared with the control group and results as shown in **Table 3.**

TABLE 3: EFFECT OF ASPARTAME ON GLUTATHIONE REDUCTASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Groups	HP	CC	CB	PM
C	3.811 ± 0.342	5.291 ± 0.299	4.771 ± 0.37	3.517 ± 0.384
ASP	3.121 ± 0.244*	4.587 ± 0.297*	3.984 ± 0.263*	2.944 ± 0.237*
D	2.602 ± 0.154 $^{\Psi}$	3.714 ± 0.166 $^{\Psi}$	3.401 ± 0.308 $^{\Psi}$	2.121 ± 0.294 $^{\Psi}$
D+ASP	2.139 ± 0.211$^{\#}$	3.196 ± 0.163$^{\#}$	2.688 ± 0.301$^{\#}$	1.411 ± 0.176$^{\#}$

HP: Hippocampus, CC: Cerebral cortex, CB: Cerebellum, PM: Ponsmedulla. C: Control, ASP: Aspartame, D: Diabetes, D + ASP: Diabetes + Aspartame. Values are Mean ± SEM of n= 6 rats. Values are significantly different from control group * Ψ # $p < 0.05$.

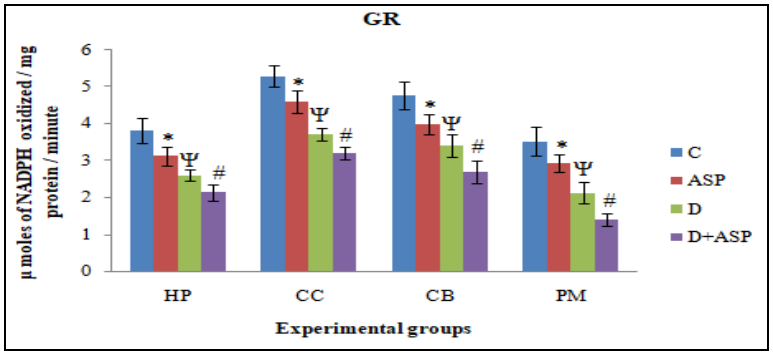

FIG. 3: EFFECT OF ASPARTAME ON GLUTATHIONE REDUCTASE ACTIVITY IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Lipid Peroxidation (LPD): The present results clearly demonstrated that the significant elevated ($p < 0.05$) in the malondialdehyde (MDA) levels was observed in ASP and Diabetes group rats when compared to the control group **Fig. 4**.

TABLE 4: EFFECT OF ASPARTAME ON MALONDIALDEHYDE LEVELS IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

Groups	HP	CC	CB	PM
C	36.741 ± 1.131	33.3 ± 1.986	31.716 ± 1.206	28.991 ± 1.795
ASP	39.908 ± 1.036*	38.6 ± 2.231*	35.65 ± 1.691*	33.683 ± 1.411*
D	44.658 ± 1.032 $^{\Psi}$	47.2 ± 2.952 $^{\Psi}$	42.30 ± 2.049 $^{\Psi}$	37.833 ± 1.956 $^{\Psi}$
D+ASP	51.258 ± 1.416$^{\#}$	54.841 ± 2.398$^{\#}$	51.35 ± 3.131$^{\#}$	44.2 ± 2.19$^{\#}$

HP: Hippocampus, CC: Cerebral cortex, CB: Cerebellum, PM: Ponsmedulla. C: Control, ASP: Aspartame, D: Diabetes, D+ASP: Diabetes + Aspartame. Values are Mean ± SEM of n= 6 rats. Values are significantly different from control group * Ψ # $p < 0.05$.

Interestingly, the results in ASP-administered Diabetes (D+ASP) group rats showed significantly elevated ($p < 0.05$) MDA levels in HP, CC, CB and PM of brain regions compared with control group. This indicates ASP severely affects the LPD levels in the brain regions and the data shown in **Table 4**.

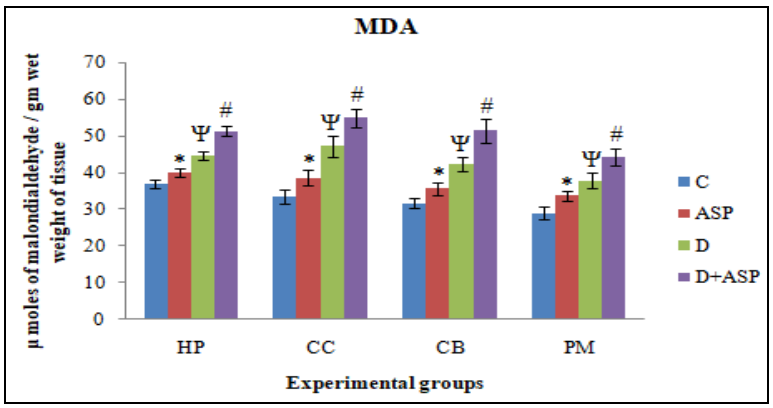

FIG. 4: EFFECT OF ASPARTAME ON MALONDIALDEHYDE LEVELS IN DIABETES-INDUCED MALE ALBINO RATS BRAIN REGIONS (HIPPOCAMPUS, CEREBRAL CORTEX, CEREBELLUM AND PONSMEDULLA)

DISCUSSION: Aspartame is an artificial sweetener that is frequently used in the food sector, low-calorie meals, and soft drinks [26]. It was added to foods to enable consumers to experience a sweet taste without consuming the calories associated with sugar, assist in glycemic control, and prevent weight gain [27]. This study observed the toxic effect of aspartame in diabetic-induced rats; the digestive system immediately absorbs the aspartame and releases the metabolites phenylalanine, aspartic acid, and methanol [28]. Due to these, over-production of free radicals occurs and causes disturbance to the natural scavenger process, and results in oxidative stress [29]. Aspartame metabolites methanol effects highly in the blood plasma and causes the generation of free radicals in the brain [30].

Antioxidant activity depletion occurs through the formation of ROS in the brain regions [31]. ROS role is important in the defence mechanisms in pathological conditions, but the excess ROS production causes tissue damage [32]. ROS production occurs continuously in the nervous system, which imbalances regular metabolism and neuronal activities. Due to high oxygen consumption, brain tissues are highly sensitive to oxidative stress. ROS majorly involved in several neurological diseases (Parkinson's, Alzheimer's, and Schizophrenia) [5]. Diabetes is associated with higher oxidative stress. ROS-induced damage to the insulin-producing pancreatic beta-cells induces diabetes. Diabetes arises from the irreversible destruction of pancreatic beta cells, causing degranulation and reduction of insulin secretion [32]. The present research work was carried out to evaluate the aspartame effect on diabetes-induced male albino rats. The antioxidant defence system enzymes SOD and CAT showed lower activity in the hippocampus, cerebral cortex, cerebellum and pons medulla brain regions. In the experimental group's aspartame (ASP) group, diabetes (D) group animals showed significantly declined antioxidant activity of SOD and CAT compared with control group rats. Further, interestingly the investigation of aspartame administered diabetes group (D+ASP) showed significant lower antioxidant activities of SOD and CAT in the brain regions.

The lower activity of SOD and CAT could also be due to their decreased protein expression in Diabetes condition [33]. The decline in antioxidant enzyme activity SOD, CAT, GPx, GR, and GSH could be due to the harmful effect of free radicals produced after methanol exposure, or it could be a direct effect of formaldehyde released during methanol oxidation on these enzymes [34]. In the present study, we observed novelty in the aspartame-administered diabetes group rats (D+ASP) group rats antioxidative enzymes SOD and CAT activity significantly very low due to the aspartame metabolites of methanol and its products formaldehyde and formate. Generally, diabetes rats are in decreased antioxidative defence system; to these rats aspartame (50 mg/kg body weight) oral administered showed more effect on the brain antioxidative defence system. Above mentioned previous studies also support our results. SOD acts

as the first line of defence against toxic cellular oxyradicals by dismutating superoxide radicals into H_2O_2. This is subsequently reduced by catalase in the system SOD protects the catalase from superoxide anion inhibition. Catalase inversely protects SOD inactivation by H_2O_2. Specifically, mislocalized CAT is correlated with the accumulation of H_2O_2 and other ROS in the cells that compromise neurological function [35].

As a result, CAT deficiency or dysfunction is thought to have a role in the aetiology of many age-related degenerative disorders. The antioxidant system plays a crucial role in the removal of peroxide radicals and superoxide generated in the tissues [36].

We found that the GR activity was decreased in ASP group rats with 50 mg/kg b.w. of oral aspartame administration and in diabetes (D) group. Here in aspartame-administered diabetes (D+ASP) group, rats showed significantly very low activity of GR in the brain regions of the hippocampus, cerebral cortex, cerebellum, and pons medulla. This is due to the aspartame metabolite methanol effect on the antioxidant system and diabetes releasing free radicals on the brain's antioxidant system. In the antioxidative system of the diabetic group, oral aspartame administration significantly impacts its toxic metabolites. Lower activity of GR indicates the production of LPD and elevated levels of H_2O_2 production.

The decrease in GR activity could indicate a lack of oxidized glutathione synthesis from GSH mediated by GPx. The decline in enzyme activity can be attributed to the action of methanol metabolites like formaldehyde and free radicals. The hydroxymethyl derivatives produced by the formaldehyde reaction can form intra- and intermolecular bridges in proteins. At the same time, free radicals formed during methanol oxidation can also cause protein peroxidation. As a result of these changes, proteins may become denatured, aggregated, and fragmented, altering their physicochemical properties and possibly losing their catalytic activity [37]. In the present investigation, it was recorded that LPD levels in various brain regions, viz. Hippocampus, Cerebral cortex, Cerebellum, and Pons medulla were significantly increased in the aspartame administered (ASP) group, Diabetes (D) group compared with control (C) group rats. Simultaneously in the four brain regions, aspartame administered diabetes group (D+ASP) showed significantly elevated LPD levels compared with the control, ASP, and D groups. Aspartame metabolites show an additional effect in diabetes-induced albino rats. The increased LPD concentration in the brain specifies that the brain is susceptible to LPD in Diabetes. This is due to increased oxidative stress and decreased antioxidant systems.

Lipid peroxidation, or the reaction of oxygen with unsaturated lipids, produces a wide variety of oxidation products, such as lipid hydroperoxides (LOOH). Among the many different aldehydes that can be formed as secondary products during lipid peroxidation include malondialdehyde (MDA) [38]. The study by Mourad (2011) supports our current finding that oral administration of aspartame (40 mg/kg) resulted in a significant elevation of LPO in the liver [39]. Antioxidant defence mechanisms for metabolite detoxification are essential because their function changes the brain's susceptibility to the harmful effects of ROS. The present study reveals that aspartame ingestion in the normal and diabetic rats results in elevated free radicals and an unbalanced antioxidant status in the brain.

CONCLUSION: In conclusion, our present findings believe that the changes in the antioxidative system of the brain by aspartame consumption are dose-dependent. Individuals with diabetes mellitus, obesity, pregnancy, children, and breastfeeding individuals are the major consumers of aspartame in their daily lives. Therefore, neurobiological changes observed in this study should be thoroughly Explored. Since, aspartame safety is becoming a bigger issue for the health-conscious population.

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CONFLICT OF INTEREST: The authors have no conflicts of interest in this study.

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