SPIRULINA SUPPLEMENTATION DURING PRENATAL PROTEIN DEPRIVATION AFFECTS THE NEUROCOGNITIVE DEVELOPMENT OF RATS' F1 OFFSPRING

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ABSTRACT
The study of protein malnutrition (PMN) or protein-calorie malnutrition (PCM) is gaining popularity, owing to the fact that it has an impact on the brain's neurotransmitters, enzymes, and structural proteins. If the mother's diet is lacking in protein, it is possible that her foetus may be born with developmental delays. Because of this, inadequate nutrition for the expectant woman is a significant contributor to prenatal mortality and morbidity. Studies conducted over the past few years have shown a significant relationship between eating habits and mental health, highlighting the linear nature of the relationship between the two variables. According to recent findings from our study, babies born to protein deficient mothers show physical slowness, delayed reflex ontogeny, hyperactivity, poor habituation, low anxiety, weak forelimb neuromuscular strength, and reduced cognitive functioning.

1.INTRODUCTION

1.1 OVERVIEW

Protein malnutrition (PMN) is a kind of brain injury that may occur during pregnancy, during delivery, and after birth. It can have long-term consequences on brain development. Many people in impoverished nations, particularly in Sub-Saharan Africa and South Asia, suffer from malnutrition as a result of a lack of adequate food supplies. It has been shown that malnutrition caused by a low protein diet or an insufficient protein intake during the critical period of brain development when these processes take place has an adverse effect on neuronal proliferation, myelination, synaptogenesis, and sensorimotor development in infants and children.
In order for the foetus and infant to be healthy, it is necessary for the mother to have enough nutrition during her pregnancy and breastfeeding. If the kids are well-nourished throughout both of these formative stages, they will have a more favourable birth outcome and will lay the groundwork for their long-term health. When it comes to transplacental communication and embryo development, the immune systems of the mother and the foetus must be able to communicate with each other in both directions at the same time. Pregnant women are more susceptible to nutritional deficiencies than nonpregnant women because of the increased nutritional requirements of a developing baby. A sufficient protein supply is essential for the development and proper functioning of the nervous system. It has been shown in a number of studies that protein supplementation may reduce the likelihood of having a baby with a low birth weight. The results of recent study indicate that intrauterine protein restriction has a negative impact on the behaviour of children, including delayed physical development, reduced desire and anxiety, insufficient neuromuscular strength, and depression-like behaviour. Maternal malnutrition has been related to a variety of disorders, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia (over or undernutrition). Children's higher levels of proinflammatory cytokines, as well as their disturbed neuroendocrine system, hypothalamic circuitry, and neuroimmune signalling, may all have a role in the development of metabolic illnesses. In both epidemiological and experimental studies, malnutrition has been shown to be associated with metabolic diseases such as diabetes, glucose intolerance, and cardiovascular disease (CVD). As a result of antigens from the placenta and uterus, the mother's immune system directs the growth and development of the foetal central nervous system. A mother's nutritional status before, during, and after pregnancy has an impact on the placenta's ability to provide nutrients, hormones, and immunological factors to her growing baby. This is due to the interaction between the developing immune system and the mother's nutritional status before, during, and after pregnancy. Maternal protein restriction promotes neuronal degeneration and has long-term, irreversible impacts on an organism's endocrine and behavioural profiles, according to new research. Additionally, studies on the PMN model have shown alterations in the cellular, metabolic, and neurotransmitter systems, as well as changes in behavioural and cognitive abilities of the participants. In the

presence of maternal protein shortage, infant reflexes, cognitive abilities, astrogenesis, and oligodendrogenesis were all delayed, as were myelination and myelination-related processes. Furthermore, early life plasticity and foetal programming may be the most effective explanations for the relationship between prenatal and postnatal nutritional status and adult disease progression.

2.LITERATURE REVIEW

Sorrenti, Vincenzo & castagna (2021) Many nutrients and non-nutrient compounds in Spirulina microalgae contribute to brain health. Spirulina's ability to improve brain health has been shown in several in vivo studies, with the antioxidant, anti-inflammatory, and neuroprotective effects all receiving particular attention. Spirulina has also been shown to decrease mental tiredness, protect the arterial wall of brain arteries from endothelial damage, and control internal pressure, all of which contribute to the prevention and/or mitigation of cerebrovascular disorders in preclinical trials. In addition, spirulina seems to improve motor, verbal, and cognitive abilities in malnourished children, indicating a reinforcing function in developmental processes. Evidence that spirulina plays a fundamental role in regulating hunger has been found. If you're looking to prevent or mitigate brain problems, this review will help you understand how "superfood" spirulina microalgae may do so by emphasising its nutritional worth and offering the most up-to-date information on important molecular pathways.

Sinha, Shrstha (2020) Protein malnutrition (PMN) is a worldwide health problem, although it is more widespread in Africa and Asia than everywhere else in the world. It has a negative impact on both the structure and function of the hippocampus circuitry. There is still a great deal of mystery around how maternal nutritional supplementation during starvation impacts glial cells and neurons, despite mounting evidence that PMNs alter the neurological system. Maternal Spirulina supplementation has been shown to protect the hippocampus of F1 progeny against PMN-induced reactive gliosis, oxidative stress, and neuronal injury. 15 days before conception, healthy Sprague Dawley females (n = 24) aged three months were placed on either a normoprotein (NC; 20% protein) or a low protein (LP; 8% protein) diet. As a result of Spirulina supplementation (400 mg/kg/b.wt. orally during gestation and lactation), the NC and LP group females were separated into two groups: a normal control group (NC SPI) and a lower protein group (LP SPI) (LP SPI). In this investigation, only F1 progeny were employed. As a result, the present study builds on earlier findings that Spirulina supplementation improved neurobehavioral and cognitive abilities in protein-deprived rats, and it found that maternal Spirulina consumption partially prevented PMN-associated neuropathological alterations in terms of reduced reactive gliosis and apoptotic cell population, improved dendritic connectivity, and decreased oxidative damage. The findings show that maternal Spirulina supplementation partly restores cellular abnormalities in the hippocampus following PMN, and that Spirulina-based interventions against malnutrition may be in the works.

Sinha, Shrstha & Nisha (2019) Adversities in early childhood (stress, illness, and malnutrition) may have long-term effects on the brain's neurocognitive, hippocampus, and immune systems. Neurocognitive impairments and psychopathologies in adolescence and adulthood in kids may be linked to maternal protein deficiency. Low and middle-income countries are particularly vulnerable to maternal malnutrition. The purpose of this study was to examine the effects of dietary Spirulina supplementation on the reflex, neurobehavioral, and cognitive development of the offspring of protein malnourished mothers during pregnancy and lactation. Protein-rich Cyanobacterium is widely utilised as an anti-aging nutraceutical and to treat neurodegenerative conditions such as Alzheimer's disease. Prior to conception, Sprague Dawley rats were fed either a low-protein (8% protein) or normal-protein (20%) diet for 15 days. Spirulina (400 mg/kg/bwt) was given to pregnant women from the time of conception through the time of breastfeeding. A number of factors were evaluated in the F1 offspring, including the dams' ability to reproduce, the offspring's physical development, the offspring's postnatal reflex ontogeny, the offspring's locomotion and neuromuscular strength, as well as their anxiety and anhedonic behaviour. Results from the study showed that Spirulina supplementation improved the reproductive performance of protein-malnourished dams, which in turn resulted in faster acquisition of neurological reflexes, a better physical appearance and an increase in neuromuscular strength as well as an improvement in spatial learning and memory. Reduced microglial activation was shown to go along with these positive effects of Spirulina ingestion, which may help restore behavioural and cognitive abilities in protein-malnourished F1 rats. So Spirulina supplementation for pregnant women might help alleviate malnutrition-related behavioural and cognitive deficiencies in their children.

Sinha, Shrstha & Nisha (2018) It has long been acknowledged that malnutrition is a major impediment to the development of impoverished and developing nations across the world. To reduce the risk of malnutrition-related stress in adulthood, maternal, neonatal, and postnatal nutritional immunity may be used. In particular, the nutritional state of the mother is a significant factor in determining the health of her child in the long run. Children who are born to malnourished mothers have a higher mortality rate, weakened immune systems, stunted motor development, and cognitive impairments as a result. Nutraceuticals may be utilised as an effective immunomodulatory intervention to improve immunity against infections. In early life, the immune system has a tremendous dynamic potential to control both genetic and environmental processes and to adjust to rapidly changing environmental exposures. Because of the early life flexibility of the immune system, these immunomodulatory stimuli or powerful nutraceutical strategies may be able to enhance immunity against infectious illnesses caused by malnutrition. Protein deprivation may have long-lasting consequences on CNS development, oxidative stress and inflammation as well as related behavioral/cognitive deficits. This review presents substantial human and animal research on this topic. Spirulina as a powerful protein source and neuroprotectant against protein malnutrition (PMN) related adverse alterations have also been highlighted in relevant research on nutritional supplementation and rehabilitation. But there are numerous difficulties that need to be addressed in the future in order to properly modulate these therapeutic approaches to avoid malnutrition.

Hernandez, Alejandro & Burgos (2008) It has been shown that pregnant rats' offspring's long-term potentiation (LTP) is affected when the protein content is reduced from 25 to 8 percent casein in their diets. The goal of this research was to see whether the plastic properties of the EC in the adult progeny might be altered by this form of maternal starvation. Neither the ipsilateral occipital cortex nor the CA1 hippocampal area of prenatally malnourished 55–60-day-old rats developed LTP in the medial EC to tetanizing stimulation as did normal eutrophic controls. BDNF concentrations in the EC of starved rats were not increased by tetanizing activation of CA1. Adult prenatally malnourished rats may have an impaired ability to produce long-term potentiation (LTP) and to raise BDNF levels, which may contribute to their poor learning performance.

3. WARNING: GRAPHIC CONTENT MAY OFFEND SOME READERS; READ THE INTERACTIVE DOCUMENT FOR DETAILED INFORMATION

The brain's bioenergetic and antioxidant defence processes are intertwined with the brain's glia. As compared to other bodily systems, the neurological system is more prone to oxidative stress-induced damage because of the limited replacement of injured brain cells, the high oxygen demand, the availability of redox-active metals, and the presence of polyunsaturated fatty acids Reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the central nervous system (CNS) are produced and scavenged at different rates, resulting in free radical attack on neural cells. This leads to pathological changes in the brain that accompany ageing and neurological disorders such as Alzheimer's, Parkinson's, and Huntington's diseases, as well as amyotrophic lateral sclerosis.

Deficiency in protein has been linked to an increased risk of oxidative stress, perhaps owing to an imbalance in the homeostatic balance between prooxidants and antioxidants. Catalase (CAT), superoxide dismutase (SOD), plasma glutathione, and total plasma proteins are all changed in malnourished stunted children, as are the levels of malondialdehyde (MDA) and nitric oxide. The release of inflammatory cytokines and chemokines is promoted by reactive species, which may damage DNA and activate signalling pathways that lead to glial activation and neuronal damage. The oxidative stress or imbalance caused by these reactive species has been linked to the advancement of neurological diseases. The pathophysiology of schizophrenia has been linked to oxidative stress in many studies. This includes high levels of oxidative stress index (OSI) and decreased antioxidant enzyme and nonenzymatic activity in red blood cells, serum and cerebrospinal fluid.

Anti-inflammatory and anti-oxidant properties of a wide range of nutraceuticals and medicines have been thoroughly studied. Spirulina has been shown to protect the central nervous system (CNS) by lowering signs of inflammation and oxidative stress, and as a result, to lessen neurological impairments when taken as a supplement. The amount of carotenoid, chlorophyll, phycocyanin, and phycobiliprotein in Spirulina is connected with its antioxidant properties. Spirulina supplementation improves spatial and motor learning in senile rats by favourably modulating cerebellar glutathione levels and reducing malondialdehyde levels and pro-inflammatory cytokines. Antioxidant and anticyclooxygenase-2 actions of phycocyanobilin and phycocyanin found in Spirulina diminish peroxynitrite-induced DNA oxidative damage. Using an eight-week strength training programme in rats, de Freitas Brito et al. (2020) found that Spirulina platensis improved exercise-induced performance deficits, muscle damage, inflammation, and oxidative stress, suggesting that Spirulina might be used as a nutritional supplement in sports. Spirulina supplementation may be useful to individuals with oxidative stress, especially those with neurological illnesses and malnutrition, according to the results of this study.

Since PMN-associated neurobehavioral and cognitive impairments are thought to be caused by oxidative imbalances, the current goal was to examine the potential protective effects of maternal Spirulina supplementation against these imbalances, using neurochemical measurements of MDA, SOD and CAT activity as a guide. This could help us better understand the efficacy of Spirulina. i.e.,

3.1 Neurochemical procedures

Experiments were conducted on the offspring of NC, NC SPI, LP, and LP SPI dams (F1 generation) as outlined in the section 'Experimental design and nutritional content of experimental diets' Cervical dislocation was used to end the lives of four animals from each age group at one, three, six, and twelve months. Once brains were cut open and hippocampus tissue was properly extracted, neurochemical estimations could be made. Using BSA as a reference, the protein content of hippocampus tissue was first calculated using Lowry's technique. Hippocampal tissues were then tested for MDA, SOD, and CAT levels. To examine the neurochemical data, all procedures were conducted twice and the means were determined.

3.2 Statistical analysis

GraphPad's Prism 5.0 was used to calculate all of the statistics, and the results are shown as mean standard error of the mean (SEM) (SEM). ANOVA, followed by the Bonferroni post-hoc test, was used to examine the data in two ways. In all assessments, p 0.05 was considered statistically significant. using GraphPad Prism, the mean and standard deviation of the mean were plotted.

4. RESULTS

4.1 Supplementation with Spirulina reduces lipid peroxidation

The molecular measure of oxidative stress, MDA, is widely accepted as the end result of polyunsaturated fatty acid peroxidation in cells. All four groups had MDA levels measured biochemically in their hippocampus tissues to detect oxidative stress. Researchers found that PMN rats' hippocampus MDA levels were up substantially compared to those of well-nourished rats, suggesting that LP F1 rats had suffered from oxidative brain damage as well. Supplementation with spirulina reduced PMN-related brain damage by lowering MDA levels in hippocampus tissues of LP SPI F1 rats aged 1, 3, 6, and 12 months (Table 1).

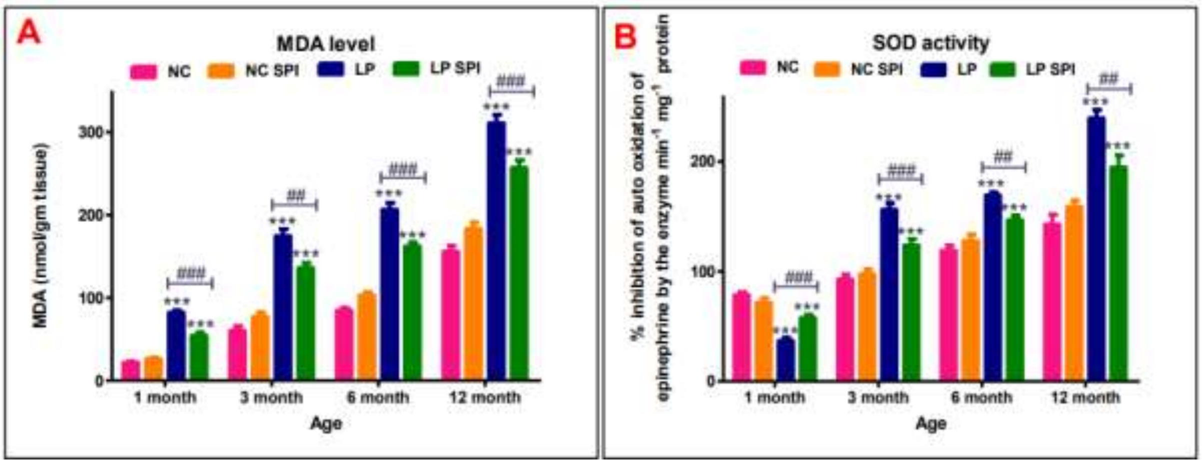
Table 1: MDA, SOD, and CAT activities are listed in the table mean ± SEM

	1 month	3 month	6 month	12 month
MDA level NC	21.73±1.28	60.46±5.09	84.77±3.13	155.8±6.49
(nmol/gm tissue) NC SPI	26.15±1.55	77.12±5.31	111.8±5.43	183.5±7.29
LP	82.10±2.67	174.5±8.38	206.4±8.37	310.7±10.28
LP SPI	54.19±3.71	136.1±6.13	161.9±4.86	256.8±9.30
SOD activity NC	78.54±2.20	92.84±4.25	118.9±4.58	142.8±8.86
(% inhibition of auto oxidation of epinephrine by NC SPI	71.53±4.30	97.83±4.29	128.1±5.52	158.9±5.58
the enzyme min^{-1} mg^{-1} protein) LP	36.91±2.65	156.3±5.69	169.1±2.77	239.4±7.70
LP SPI	57.72±2.87	123.8±5.60	146.7±4.05	194.6±10.80
CAT activity NC	2.48±0.27	3.49±0.15	3.80±0.18	4.21±0.11
(µmole H_2O_2 decomposed min^{-1} mg^{-1} protein) NC SPI	2.12±0.18	3.18±0.16	3.35±0.19	4.20±0.12
LP	0.60±0.09	2.13±0.11	2.77±0.17	3.15±0.11
LP SPI	1.33±0.06	2.91±0.04	3.11±0.31	3.72±0.10

Both maternal protein intake and Spirulina supplementation had a substantial impact on lipid peroxidation, according to a two-way ANOVA analysis. A Bonferroni post-hoc analysis revealed that the MDA levels in LP SPI F1 rats were lower than those in LP F1 rats [$t = 7.90$, $p < 0.001$; $t = 4.26$, $p < 0.001$; $t = 5.47$, $p < 0.001$; $t = 4.49$, $p < 0.001$] than in LP F1 rats. MDA levels in NC SPI F1 rats did not change significantly when Spirulina supplementation was given to them. From 1 month to 12 months, the MDA level was raised in all four groups. According to Fig. 39A, the findings are shown (Table 2).

Table 2 Spirulina supplementation and maternal dietary protein levels, as well as their relationship with MDA, SOD, and CAT levels are shown in the following table

MDA level (nmol/gm tissue)				
Factors	**1 month**	**3 month**	**6 month**	**12 month**
Maternal dietary	$F_{(1, 28)} = 313.5$	$F_{(1, 28)} = 184.9$	$F_{(1, 28)} = 223.3$	$F_{(1, 28)} = 181.2$
protein level (MDPL)	$p< 0.001$	$p< 0.001$	$p< 0.001$	$p< 0.001$
Spirulina	$F_{(1, 28)} = 22.13$	$F_{(1, 28)} = 2.919$	$F_{(1, 28)} = 2.311$	$F_{(1, 28)} = 2.388$
Supplementation (SS)	$p< 0.001$	$p>0.05$	$p>0.05$	$p>0.05$
Interaction between	$F_{(1, 28)} = 41.92$	$F_{(1, 28)} = 18.72$	$F_{(1, 28)} = 38.74$	$F_{(1, 28)} = 23.17$
MDPL and SS	$p< 0.001$	$p< 0.001$	$p< 0.001$	$p< 0.001$
SOD activity (% inhibition of auto oxidation of epinephrine by the enzyme min^{-1} mg^{-1}protein)				
Factors	**1 month**	**3 month**	**6 month**	**12 month**
Maternal dietary	$F_{(1, 28)} = 79.91$	$F_{(1, 28)} = 79.82$	$F_{(1, 28)} = 62.79$	$F_{(1, 28)} = 61.29$
protein level (MDPL)	$p< 0.001$	$p< 0.001$	$p< 0.001$	$p< 0.001$
Spirulina	$F_{(1, 28)} = 4.862$	$F_{(1, 28)} = 7.553$	$F_{(1, 28)} = 2.340$	$F_{(1, 28)} = 2.88$
Supplementation (SS)	$p< 0.05$	$p< 0.05$	$p>0.05$	$p>0.05$
Interaction between	$F_{(1, 28)} = 20.19$	$F_{(1, 28)} = 14.03$	$F_{(1, 28)} = 13.13$	$F_{(1, 28)} = 12.99$
MDPL and SS	$p< 0.001$	$p< 0.001$	$p< 0.01$	$p< 0.01$
CAT activity (μmole H2O2 decomposed min-1 mg-1 protein)				
Factors	1 month	3 month	6 month	12 month
Maternal dietary	$F(1, 28) = 57.73$	$F(1, 28) = 21.17$	$F(1, 28) = 7.841$	$F(1, 28) = 19.02$
protein level (MDPL)	$p< 0.001$	$p< 0.001$	$p< 0.01$	$p< 0.001$
Spirulina	$F(1, 28) = 1.093$	$F(1, 28) = 8.68$	$F(1, 28) = 0.64$	$F(1, 28) = 5.331$
Supplementation (SS)	$p>0.05$	$p<0.01$	$p>0.05$	$p<0.05$
Interaction between	$F(1, 28) = 9.59$	$F(1, 28) = 8.269$	$F(1, 28) = 3.019$	$F(1, 28) = 7.488$
MDPL and SS	$p< 0.01$	$p< 0.01$	$p>0.05$	$p< 0.05$



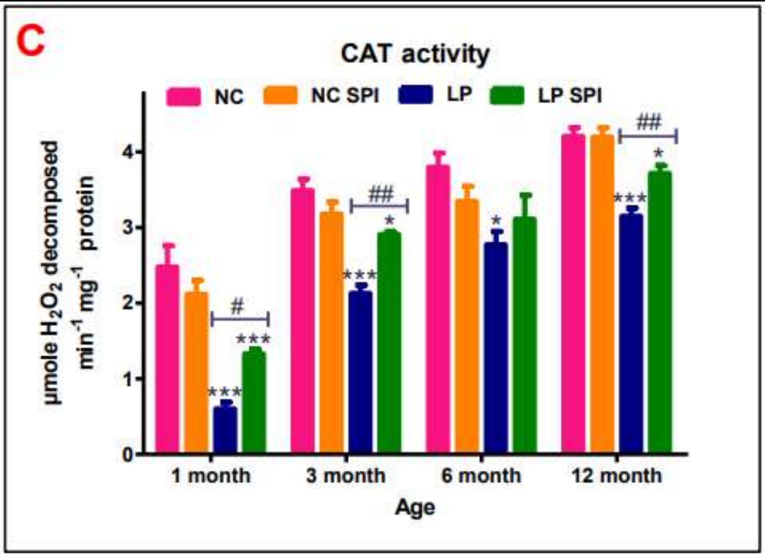


Fig. 1 Antioxidant enzyme activity in the hippocampus was reduced by Spirulina in the presence of PMNs: PMN-induced high MDA levels (A) are reduced by supplementation with Spirulina, which also has a favourable effect on the activity of the SOD and CAT enzymes. The data is shown as mean standard error of the mean (SEM). When compared to the control group, the following results are statistically significant: According to the results of the statistical tests, there were no statistically significant differences between the two groups

4.2 SOD and CAT activity are affected by Spirulina supplementation

Both SOD and CAT breakdown hydrogen peroxide (H2O2) and water into oxygen and molecular oxygen as their first line of defence against superoxide radicals. Spirulina's antioxidant properties were studied by examining the levels of SOD and CAT in hippocampus tissue. At one month of age, protein restriction in LP F1 rats resulted in a drop in SOD levels compared to normoprotein fed rats, which suggests an ineffective antioxidant defence mechanism. It is possible that protein impoverished rats' improved hippocampus SOD activity at 3, 6, and 12 months of age might reflect a compensatory rise in SOD levels in response to the chronically elevated lipid peroxidation in the protein deficient rats. An increase in the SOD level was seen at 1, 3, 6, and 12 months of age after supplementation with Spirulina. A rise in SOD activity in LP SPI F1 rats in early and late adulthood may have been a reaction to the elevated levels of MDA in NC F1 rats. Although SOD activity in LP SPI F1 rats was not as high as in malnourished rats at 1, 3, 6, and 12 months of life, this shows that Spirulina is capable of favourably sustaining antioxidant defence enzyme activity.

SOD activity was shown to be significantly influenced by the amount of protein consumed by the mother, the amount of Spirulina supplemented, and the relationship between the amount of protein consumed by the mother and the amount of Spirulina supplemented. From 1 month to 12 months of age, SOD activity rose in all four groups, which might be interpreted as an effort to counteract the age-related rise in lipid peroxidation end-products. Post-hoc analysis revealed a significant difference in SOD levels between LP F1 and LP SPI F1 rats at 1 month [$t = 4.73$, p 0.001], 3 months [$t = 4.59$, p 0.001], 6 months [$t = 3.64$, p 0.01] and 12 months [$t = 3.74$, p 0.01], indicating that Spirulina has the ability to positively modulate SOD activities.

Both at the ages of 1, 3, and 12 months, LP F1 rats had lower CAT activity in their hippocampus tissues compared to NC F1 rats. Both maternal dietary protein level and Spirulina supplementation had a significant impact on CAT activity by two-way ANOVA, as did the interaction between maternal dietary protein level and Spirulina supplementation. As a result, CAT activity in hippocampal tissues was elevated in all age groups from one month to a year old. Dietary Spirulina supplementation to protein-malnourished dams significantly improved CAT activity by one and three months at [$t = 2.92$, p 0.05], three and twelve months at [$t = 3.56$, p 0.01] and non-significantly at six months of age at[$t=1.04$, $p> 0.0.05$], suggesting increased activity of the antioxidant defence enzymes following maternal Spirulina supplementation.. Spirulina supplementation during pregnancy and lactation effectively prevents PMN-induced oxidative brain damage by lowering MDA levels and modifying SOD and CAT activities, according to the results of this study (Fig. 1B, C; Table 1, 2).

5.CONCLUSION

Oxidative brain damage may be prevented by maternal Spirulina supplementation to protein deficient dams, according to the findings of a neurochemical evaluation of antioxidant functionality in hippocampus tissues. Nutraceuticals with high levels of antioxidants, therefore, may be useful in treating neurological illnesses in which oxidative stress is thought to play a regulatory function.

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