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TREATMENT OF AUTISM SPECTRUM DISORDER USING VITAMINS AND MICRONUTRIENTS: AN EXTENSIVE CLINICAL AND MECHANISTIC STUDY EVALUATE

Ranjeet Kumar[1], Mudit Kumar[2]*, Sagar Tomar[3], Rohit Kumar[4], Ashutosh Kumar[5], Archana Maurya[6]

[1]PG Research Scholar, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.
[2]Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.
[3,4]PG Research Scholar, Department of Pharmaceutical Sciences, Gurukul Kangari Deemed to be University Haridwar Uttarakhand.
[5,6]Department of Biotechnology, Bansal Institute of Engineering & Technology, Lucknow, Uttar Pradesh.

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***Corresponding Author: Mudit Kumar**
Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Uttar Pradesh University of Medical Sciences, Saifai, Etawah 206130, UP, India.
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ABSTRACT

The neurodevelopmental illness known as autism spectrum disorder (ASD) has a complex etiology. Vitamin/mineral and targeted vitamin therapy trials have been prompted by the numerous reports of nutritional deficiencies and altered metabolism (oxidative stress, methylation abnormalities, immunological dysregulation) in ASD. Goal: Examine clinical data on vitamin-based and multivitamin therapy for core and related symptoms of ASD, summarizing safety, mechanisms, and suggestions for study and practice. Methods: Narrative evidence synthesis with a focus on large observational studies, systematic reviews/meta-analyses, and randomized controlled trials (RCTs). Results: Following multivitamin or tailored vitamin therapy (e.g., folinic acid, methyl cobalamin, vitamin D), small RCTs and a number of mechanistic and cohort studies indicate improvements in metabolic biomarkers and, in certain trials, clinician-rated or parent-reported symptoms. In observational studies and meta-analyses, prenatal folic acid/multivitamin consumption is consistently linked to a lower child risk of ASD. The overall quality of the data is inconsistent: there aren't many big, long-term RCTs, and conclusions can't be drawn with certainty because to differences in populations, supplements, dosage, and outcome measures. At conventional dosages, safety statistics are typically positive; nevertheless, large doses (or imbalanced supplements) have potential and actual dangers that need to be monitored.

KEYWARD: Autism spectrum disease, multivitamin, Mental Disorders, Behaviors.

Graphical Abstract

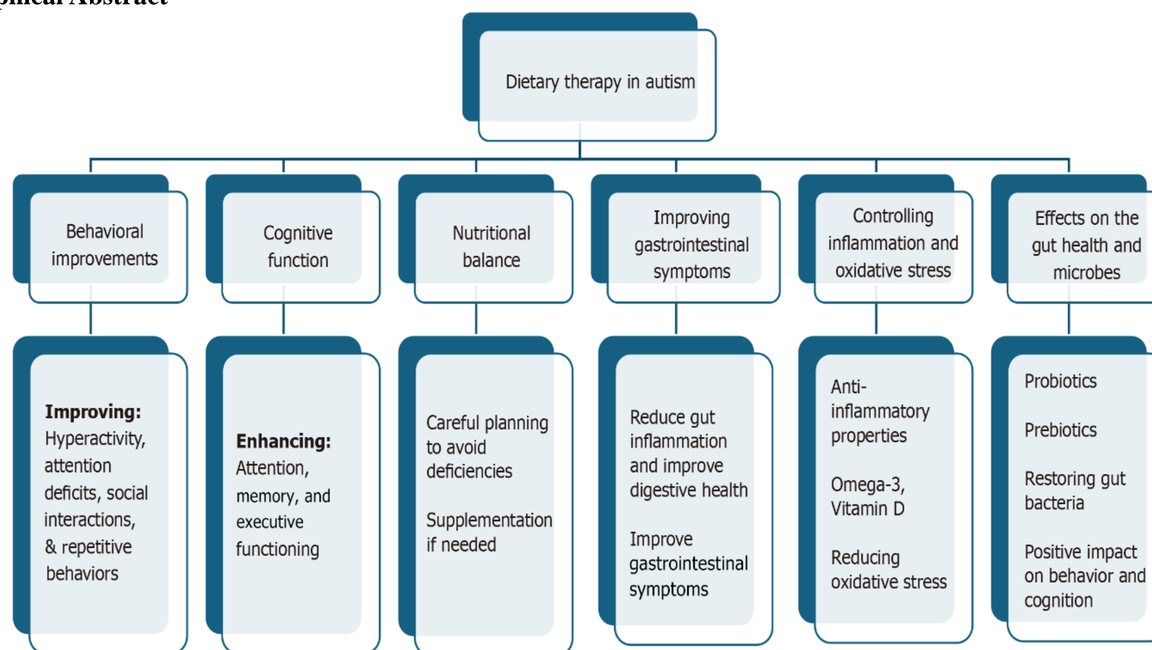

Figure-1: Abstract Overview (Dietary Therapy in Autism).

INTRODUCTION

Autism spectrum disease (ASD) affects is a serious neurological condition characterized by cognitive failure, anxiety, repetitive or stereotyped behaviors, and difficulties in social communication. In 1990, autism was officially acknowledged as a disability. According to the upcoming Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, an assessment of ASD precludes a related assessment of attention deficit hyperactivity disorder, even though metalogical hyperactivity and inattention are common in people with ASDs. An estimated 40% to 59% of children diagnosed with ASD also fit the criteria for ADHD.[1] Children with ASD have lower vitamin D concentrations than children who are usually developing, according to current epidemiological studies. Vitamin D receptors can be found in the human brain. As a neuroactive steroid, vitamin D is essential for both the growth and maturation of the brain.[2] Notably to the unclear causal relationship, the relative ineffectiveness of ASD treatment strategies, and the lack of understanding regarding the role of dietary factors in the development of ASD, researchers and caregivers are currently exposing patients to a variety of "complementary and alternative interventions." A specific focus of several therapies is the food.[3]

A multivitamin, which includes vitamins, minerals, and other micro nutritional components, is the most widely used type of vitamin supplement. Multivitamin use has been more common in recent years due to growing health consciousness and the possible advantages of multivitamin supplements for specific demographics. Mothers who took multivitamin supplements did not significantly reduce the risk of ASD in their offspring. In these circumstances, it is difficult to draw firm conclusions about this subject. More importantly, taking multivitamin supplements is affordable, practical, and safe.[4] The term "nutraceuticals" describes the expanding practice of using food or food products to prevent or improve health. The term "nutraceuticals" was initially coined in 1989 by the US Foundation for Innovation in Medicine (FIS). FIS defines nutraceuticals as "any substance that is food or a part of food and provides medical or health benefits, including the prevention and treatment of disease.[5]

Given the substantial impact that diet can have on the health and well-being of people with autism, it is imperative to comprehend the dietary influences on ASD. Due to their sensory sensitivity, many people with ASD have limited and repetitive eating patterns, which can lead to nutritional deficiencies. Furthermore, dietary practices can have an impact on GI problems, which are prevalent in people with ASD and may worsen behavioural symptoms. Examining the connection between diet and ASD can help find nutritional interventions that work to improve overall health, improve quality of life, and alleviate some of these difficulties.[6] In addition to intestinal mucosal abnormalities and altered intestinal microbiota composition, children with ASD frequently display non-specific gastrointestinal symptoms, such as constipation, abdominal pain, and extremely restrictive diets. In light of these findings, a variety of dietary interventions have been employed as an additional therapy option for ASD, and studies and case reports in the literature demonstrate positive outcomes from the use of particular dietary supplements in these patients.[7]

The process is often associated with medical comorbidities that increase the risk of micronutrient

deficiencies, such as gastrointestinal issues, sleep disorders, and selective eating. Vitamin/mineral therapy is important because: metabolic abnormalities (oxidative stress, poor methylation, and glutathione pathways) are found; ASD cohorts frequently have low levels of vitamin D, folate/B12, and other micronutrients.[8] Periconceptional folic acid and multivitamin use by mothers reduces the risk of ASD in kids, according to observational findings. Targeted vitamin therapy (such folinic acid and methyl cobalamin) and over-the-counter multivitamin/mineral supplements are frequently used by clinicians and families; however, safety, response heterogeneity, and therapeutic efficacy must be considered.[9] Since evidence regarding various vitamins, specifically vitamins A and E, and minerals, such as iron (ferritin), iodine, and zinc, were inconsistent and conflicting, decreased vitamin D levels were consistently seen in children with ASD across numerous investigations. Significant variables influencing results included individuals, study methodology variability, and irrelevant factor regulating these supplements.[10]

MULTIVITAMIN / MINERAL SUPPLEMENTS: OPEN TRIALS AND RCTS

Small Randomized Clinical Trials: In a pilot randomized, double-blind, placebo-controlled, three-month trial (Adams & Holloway) including twenty children, a moderate-dose multivitamin/mineral supplement was found to alleviate some symptoms. Improved nutritional/metabolic biomarkers and a slight improvement on certain clinician/parent assessments were observed in larger randomized trials conducted by the same group (subsequent controlled studies). Although the evidence is based on heterogeneous preparations and small to moderate sample sizes, it is encouraging.[11] Studies and observational data: Multivitamin use is widespread (surveys show greater than fifty percent consumption), and several kids with Autistic have selective diets and deficiency in micro nutrients. Some observational studies associate supplementing with better nutritional indices, despite the lack of evidence supporting a causal association.[12]

SPECIALIZED VITAMIN TREATMENTS

Folinic acid: Frye et al.'s double-blind RCT offers solid proof that folinic acid can improve verbal communication in a subset of kids with ASD and language impairment. Benefit is indicated by secondary analysis and subsequent trials, especially in children with autoantibodies to the folate receptor or anomalies in cerebral folate metabolism. Further research is needed to determine long-term effects, however safety at examined levels looks reasonable for short-term studies.[13]

Methyl cobalamin (methyl B12): Clinician-rated benefits and correlations with enhanced methylation metabolites have been found in several placebo-controlled trials using oral or subcutaneous methyl B12; however, effects seem to vary among patients.[14]

Vitamin D: Several RCTs and meta-analyses have evaluated vitamin D supplementation in children with ASD. While some RCTs reveal improvement on particular behavioural scales and inflammatory indicators, meta-analyses show a minor effect in groups with deficits. Correcting vitamin D insufficiency is generally advised because to the significant frequency of low vitamin D in ASD cohorts.[15]

B vitamins and antioxidant cofactors: Studies on individual B vitamins (such as B6), combinations, and antioxidants (such as vitamin C and E) have produced inconsistent findings; some open trials and small RCTs report symptom improvements, but conclusive findings are impossible due to small sample sizes and heterogeneity. Several research concentrating on the methylation/glutathione pathways revealed improvements in biochemical markers after supplementation.[16]

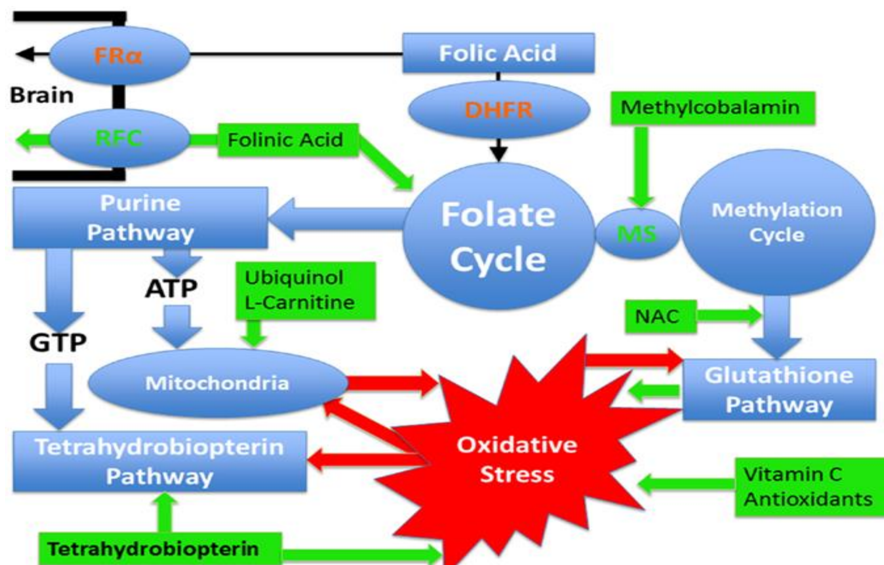

Figure-2: Vitamin Treatments Process.

FOLIC ACID AND MULTIVITAMINS DURING PREGNANCY AND THE RISK OF ASD

Numerous major observational studies and meta-analyses have shown that children whose mothers took prenatal multivitamins or folic acid throughout the periconceptional/early pregnancy stage consistently had a decreased risk of ASD. Despite being observational (not randomized) and vulnerable to residual confounding, results are similar across cohorts and meta-analyses. One of the most convincing population-level evidences showing vitamin supplementation can lower the incidence of ASD is this.[17]

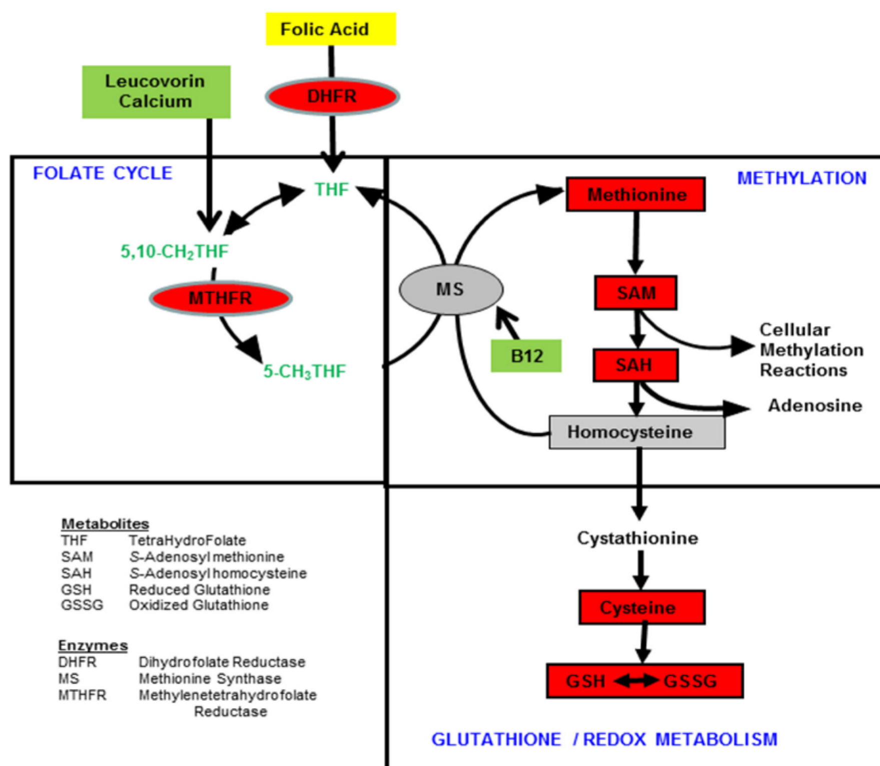

Figure-3: Folic Acid Metabolites Process.

MECHANISTIC PLAUSIBILITY

Methylation and glutathione: It have been demonstrated that many ASD cohorts have low glutathione levels and aberrant methylation; biochemical research has demonstrated that B vitamins and cofactors can restore methylation capacity. Immune/inflammation and vitamin D: The immunomodulatory effects of vitamin D and the established connections between low 25-OH vitamin D and ASD provide the biological basis for research. Folate transport and receptor autoantibodies: In some studies, brain folate insufficiency and folate receptor autoantibodies in subgroups of children with ASD account for responsiveness to folinic acid.[16]

SAFETY-RELATED FACTORS

While conventional prenatal and paediatric multivitamin dosages are generally safe, supraphysiologic dosing (high-dose folate, B6, A, etc.) might have adverse consequences and may hide other deficiencies (e.g., excessive folic acid can mask B12 insufficiency). Careful selection, administration, and monitoring—including serum levels as needed—are indicated. A few isolated theories and few data suggest that excessive multivitamin exposure in very early life may have unanticipated correlations, but the evidence is poor and unclear.[18]

IMPORTANT SUGGESTIONS (DIAGNOSTIC)

When clinically appropriate, screen children with ASD for common deficiencies (vitamin D, iron/ferritin, B12/folate), particularly those who have GI issues or restrictive eating.

Use conventional, guideline-based dosing to address recognized inadequacies (not mega doses without indication). When food consumption is insufficient, consider evidence-based formulations, steer clear of excessive single-vitamin mega doses, and think about a balanced paediatric multivitamin.

Discuss the trial findings, potential benefits in biomarker-positive subgroups, uncertain long-term consequences, and the importance of monitoring with families thinking about folinic acid, methyl B12, or other targeted medicines. Making decisions along with the child's care team is advised. According to public health recommendations, prenatal folic acid and multivitamin consumption is linked to a lower risk of ASD in observational studies and is advocated for the prevention of neural tube defects; adhere to obstetric guidelines for dosage.[19]

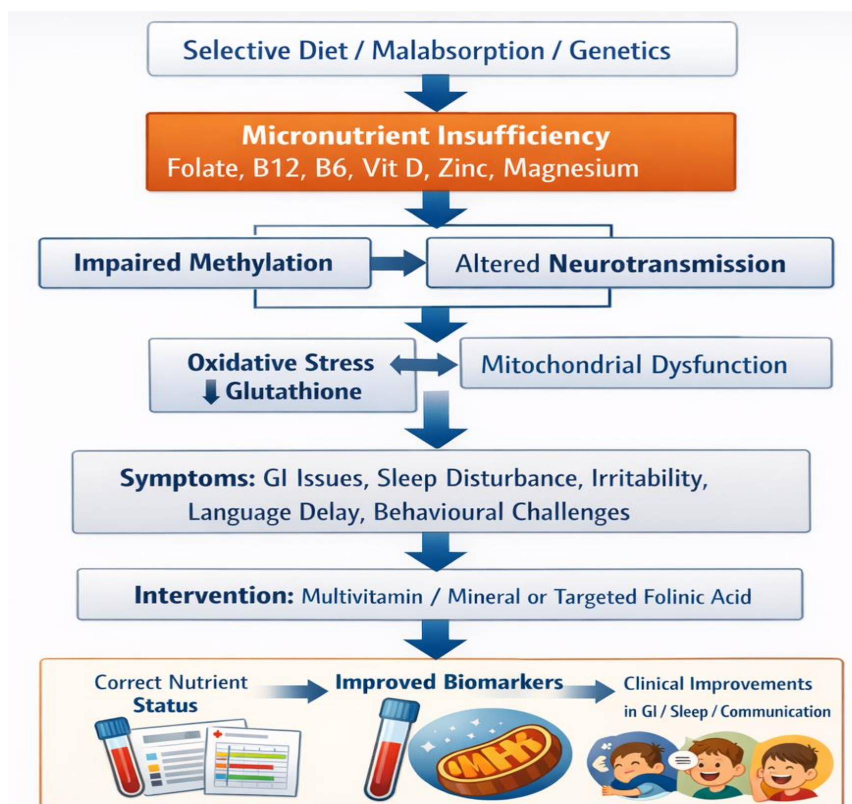

Figure-3: Micronutrient Deficiencies and Health Impact.

Table 1: The different types of vitamins used in ASD.

Vitamin	Role in human body	Probable consequence of improper level	Treatment efficiency in ASD patients	Ref.
A	Improvement of gut microbiota; increased plasma retinol, CD38, and RORA mRNA	Impairment of central nervous system development; a decrease of CARS score; increased serum 5 hydroxy tryptamine (5-HT) levels	No data available	20,21
C	Antioxidant properties; essential for proper functioning of the body; participates in enzymatic reactions	Scurvy, impaired immune function	Worse 2% No change 52% Improvement in 46%	22
D	Play a role in brain development and function, mood regulation; e.g., neuronal differentiation, axonal connectivity, dopamine ontogeny, immunological modulation; transcriptional control over a large number of genes	Deficiency may contribute to the pathogenesis of certain psychiatric disorders, e.g., depression; strong association with ASD	No data available	23,24
B_1	Essential for the proper functioning of the nervous system; participate in the metabolism of carbohydrates	CNS diseases; Wernicke-Korsakoff syndrome, beriberi; may cause language deficiency; strong association with ASD	No data available	25
B_6	Involved in neurotransmitter synthesis, gene expression; cofactor in many reactions (e.g., transamination, decarboxylation); important role in brain development	Anemia associated with depression; impaired immune function; may be associated with convulsive seizures	Alone Worse 8% No change 63% Improvement in 30% With magnesium Worse 4% No change 46% Improvement in 49%	26

B_9 Folate	Participates in the synthesis of nucleic acids; B9 essential for the proper functioning of the nervous system; helps to deal with stress; in the fetal period, folic acid regulates the development of nerve cells	Affective disorders (depression, anger)	Worse 5% No change 50% Improvement in 45%	27,28, 29,30, 31,32, 33,34, 35,36,
B_{12}	Essential cofactor in methionine transmethylation/transsulfuration metabolism	Anemia, cognitive impairment, affective Disorders (depression, anger)	Worse 6% No change 22% Improvement in 72%	37,28, 39,33, 34,35, 36

CONCLUSION

Treatment of autism spectrum disorder, vitamin and multivitamin therapy offer a viable supplementary strategy, especially for those with established nutritional deficiencies or metabolic disorders. There may be advantages in enhancing biochemical indicators and, occasionally, behavioral symptoms, according to data from observational research and clinical trials. In certain subsets of ASD patients, targeted therapies including folic acid, methylcobalamin, and vitamin D supplements have positive outcomes. Additionally, taking multivitamins and folic acid supplements during pregnancy may help lower the chance of developing ASD.

Despite these encouraging results, the present body of evidence is still constrained by inconsistent results, small sample sizes, and variation in study techniques. Consequently, it is not advised to regularly take high-dose vitamin treatments without a therapeutic indication. A tailored, evidence-based strategy with appropriate oversight is crucial. In order to further define efficacy, safety, and long-term results and eventually direct clinical practice in the therapy of ASD, future research should concentrate on large, well-designed randomized controlled trials.

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