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Original Research

Impact of Sublingual Glutathione on Oxidative Biomarkers and Behavior in Children with Autism: A Pilot Investigation with Pharmacist Involvement

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Abstract

Background: Autism Spectrum Disorder (ASD) is defined by impairments in social communication, repetitive behaviors, and cognitive variability. Oxidative stress is associated with the pathogenesis of ASD, characterized by imbalances between oxidants and antioxidants, particularly reduced glutathione (GSH). Although glutathione supplementation shows potential, its clinical efficacy remains inconsistent due to limited bioavailability when administered orally. **Objectives:** This study aimed to assess the impact of sublingual glutathione supplementation on oxidative stress indicators and behavioral outcomes in children diagnosed with ASD. **Methods:** A total of 25 children with ASD, aged 7 to 18 years, and 25 matched healthy controls participated in an open-label, pre-post intervention trial. The ASD group administered sublingual reduced glutathione for a duration of six weeks. A clinical pharmacist, member of research team, supervised supplement dispensing, provided caregiver counseling, and monitored adherence throughout the study. Serum oxidative stress markers, comprising reduced glutathione (GSH), oxidized glutathione (GSSG), GSH/GSSG ratio, total antioxidant capacity (TAC), total oxidant status (TOS), malondialdehyde (MDA), and protein carbonyl levels, were assessed at baseline, three weeks, and six weeks. evaluations utilized the Assessment of Basic Language and Learning Skills-Revised (ABLLS-R). **Results:** Baseline oxidative stress markers showed elevated stress levels and diminished antioxidant capacity in patients with ASD compared to controls ($p < 0.05$). Following the intervention, notable improvements in antioxidant status, as measured by GSH, the GSH/GSSG ratio, and TAC, were observed. Behavioral improvements were significant in specific domains, including cooperation, imitation, social interaction, visual performance, vocal imitation, play, and receptive language. **Conclusions:** Sublingual glutathione supplementation significantly elevated antioxidant levels and specifically improved behavioral functioning in children with ASD. Pharmacist involvement contributed to proper administration and adherence, supporting the effective delivery of the intervention. These data indicate the possible usefulness of antioxidant therapy in the management of oxidative stress-related symptoms in ASD. Additional randomized controlled trials are advised.

Keywords: Autism Spectrum Disorder (ASD); Sublingual glutathione; Oxidative stress; Antioxidant markers; Behavioral outcomes; Autism; Glutathione supplementation; Good health

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disease marked by diverse deficits in social communication, restricting or repetitive behaviors, and fluctuating cognitive abilities. As a spectrum disorder, ASD displays a wide array of symptom severity, with initial clinical signs generally appearing in childhood[1]. The fundamental diagnostic criteria encompass enduring deficiencies in social-emotional reciprocity, nonverbal communication, and relationship formation, in addition to inflexible adherence to routines, stereotyped behaviors, or intense interests[2].

Global epidemiological data indicates a significant rise in ASD prevalence, with current estimates suggesting that one in 127 individuals are diagnosed globally. This growing trend is partly due to the broadening of diagnostic criteria, enhanced surveillance systems, and increased public and clinical awareness. Nonetheless, various biological and environmental factors contributing to increasing incidence rates are still under investigation, requiring additional etiological research[3].

The pathophysiology of ASD is recognized as a complex interaction between genetic susceptibility and environmental factors. Although genome-wide association studies have identified various risks loci related to synaptic function and neural connection, no single genetic factor explains the heterogeneity of ASD. Simultaneously, prenatal and perinatal environmental factors—such as maternal immune activation, toxin exposure, and gestational stress—are hypothesized to interact with genetic predispositions, potentially modifying neurodevelopmental pathways[4-6].

In addition to primary symptoms, ASD often coexists with various medical and psychiatric illnesses, such as intellectual disability[7], seizures[8], gastrointestinal issues[9], sleep disruption[10],

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anxiety, and mood disorders[11]. These comorbidities exhibit significant interindividual variability, which substantially impacts adaptive functioning, social participation, and long-term outcomes. Thus, multidisciplinary management frameworks that prioritize personalized interventions and comprehensive support networks are essential for enhancing developmental outcomes and quality of life for impacted persons[12-14]

Children with ASD frequently require pharmacotherapy to manage challenging behaviors and co-occurring conditions. This makes clinical pharmacist involvement essential in ensuring safe and effective therapy. Pharmacists play a vital role in counseling ASD patients and their caregivers about each medication's purpose, proper administration, and potential side effects or interactions[15]. By providing clear guidance and closely monitoring drug therapy, pharmacists help optimize treatment outcomes and reduce adverse effects in this vulnerable population[16, 17]. They also collaborate with physicians and families as part of the healthcare team to assess therapeutic response, address issues like nonadherence, and adjust therapies as needed[18]. Such engagement not only improves medication safety but also builds trust with caregivers, which is crucial for long-term treatment success[19].

Oxidative stress, defined as an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defenses[20-23], is increasingly recognized as crucial to the etiology of ASD. Individuals with ASD frequently have heightened markers of oxidative damage, including raised levels of lipid peroxidation (malondialdehyde (MDA)), protein oxidation (protein carbonyls), and DNA damage[24]. Simultaneously, individuals with ASD exhibit decreased antioxidant capabilities, as indicated by lower levels of essential antioxidants, such as reduced glutathione GSH, total antioxidant capacity (TAC), and antioxidant enzymes, including glutathione peroxidase and superoxide dismutase. These metabolic disruptions are associated with neuroinflammation, mitochondrial dysfunction, and neurodevelopmental deficits, consequently exacerbating the cognitive and behavioral manifestations of ASD[25].

Antioxidant treatments aimed at mitigating oxidative stress in ASD, such as glutathione, N-acetylcysteine (NAC), coenzyme Q10 (CoQ10)[26], omega-3 fatty acids, and dietary supplementation with important antioxidant vitamins (C and E) and minerals (selenium), have demonstrated variable levels of efficacy[25,27-32]. Research suggests that antioxidant treatment may lead to improvements in social conduct, cognitive function, and communication skills; however, rigorous clinical trials are still necessary to confirm these results[33]. Moreover, dietary strategies aimed at augmenting antioxidant defenses may facilitate more effective management of oxidative stress, thereby enhancing the overall quality of life for patients with ASD[34].

Glutathione, a crucial antioxidant, is a tripeptide composed of glutamine, cysteine, and glycine, essential for maintaining intracellular redox equilibrium and protecting neural integrity against oxidative stress. ASD patients often demonstrate diminished GSH levels, indicated by reduced serum cysteine concentrations and a decreased GSH/GSSG ratio compared to neurotypical individuals. Such abnormalities compromise antioxidant capability, thereby increasing cellular susceptibility to oxidative damage and potentially exacerbating cognitive and behavioral issues. As a result, therapeutic strategies designed to enhance glutathione bioavailability, either directly or via its precursors and cofactors, have garnered considerable therapeutic attention[27,35].

Alternative indirect methods to elevate glutathione levels, including supplementation with NAC or cysteine-rich whey protein, have shown more consistent and substantial behavioral improvements in children with ASD, particularly in reducing irritability and enhancing adaptive behavior and socialization[29,36].

Clinical evidence suggests that oral glutathione supplementation enhances oxidative stress markers in children with ASD; however, the associated improvements in behavioral symptoms are inconsistent and vary significantly among individuals[37].

Alternative glutathione administration routes, such as sublingual delivery, have garnered scientific attention due to the low bioavailability and efficacy issues associated with oral glutathione supplementation, primarily resulting from gastrointestinal breakdown and hepatic metabolism. By passing the gastrointestinal tract and bypassing hepatic first-pass metabolism and enzymatic degradation, sublingual glutathione absorption greatly increases systemic availability and bioavailability[38-40]. There is currently little direct clinical evidence to support the use of sublingual glutathione supplementation in ASD, despite the fact that this route theoretically offers clear advantages, such as enhanced tissue absorption and more effective distribution of GSH into circulation[41,42].

Pharmacists play a pivotal role in the management of neurodevelopmental disorders such as autism, particularly in the context of emerging complementary therapies like antioxidant supplementation. With oxidative stress increasingly recognized as a contributing factor in ASD, supplements such as N-acetylcysteine and glutathione have garnered clinical interest[15]. Pharmacists contribute by educating caregivers on the safe and evidence-based use of these therapies, counseling on their potential benefits, limitations, and interactions, and ensuring proper integration with conventional treatments[18]. In pediatric care, pharmacists also address practical challenges by selecting age-appropriate dosage forms, supporting adherence through behavioral strategies and schedule adjustments, and helping families overcome access barriers[43,44]. Furthermore, pharmacists can advocate for and implement screening tools to monitor oxidative stress biomarkers, allowing for individualized antioxidant therapy[45]. Through these efforts, pharmacists enhance the safety, effectiveness, and personalization of care for children with ASD.

Consequently, exploring the clinical utility of sublingual glutathione in ASD not only aligns with current biochemical understanding but also opens new opportunities for pharmacist-

led interventions in precision pediatric care. This study aims to assess the effects of sublingual glutathione supplementation on oxidative stress biomarkers and behavioral outcomes in Jordanian children with ASD, addressing current gaps in clinical evidence and supporting the broader integration of pharmacists into neurodevelopmental care models.

MATERIAL AND METHODS

Study Design

This study employed an open-label, pre-post-intervention design to evaluate the effects of sublingual glutathione supplementation on oxidative stress biomarkers and behavioral outcomes in children diagnosed with ASD. A total of 25 children with ASD (both sexes; age range: 7–18 years), with a mean age of 12.0 ± 3.6 years and mean weight of 60 ± 12.5 kg, were recruited from the Autism Academy of Jordan and Alhadban Center for Special Needs in Amman, Jordan. Additionally, a matched control group consisting of 25 healthy children, comparable in age and sex, was recruited from Med Labs Medical Laboratory in Amman, Jordan. The mean age of the control participants was 12.3 ± 2.8 years, and their mean weight was 58 ± 10.1 kg.

Participants

This study recruited participants with ASD who had been formally diagnosed by licensed psychiatrists, psychologists, or developmental pediatricians using standardized clinical assessments. Those participants were classified as moderate to severe cases. The inclusion criteria for the ASD cohort required confirmation of diagnosis, an age range of 7 to 18 years, no prior use of vitamin supplements or antioxidant therapies within the preceding month and documented parental or guardian consent. Participants with ASD were excluded if they had concurrent neurological conditions (e.g., cerebral palsy, epilepsy), psychiatric comorbidities (e.g., bipolar disorder), or metabolic disorders such as phenylketonuria.

Control participants were age- and sex-matched neurotypical children aged 7–18 years recruited from the same geographic region. Control inclusion criteria mirrored those of the ASD group regarding supplementation history and consent requirements. Exclusion criteria for controls included language-based learning disabilities, autoimmune or genetic syndromes, and chronic medical conditions that might independently influence oxidative stress pathways, as determined through clinical evaluation. Both groups underwent identical screening protocols to ensure comparability in baseline health parameters.

Ethical Considerations

Ethical approval was obtained from the ethics committee of the Deanship of Scientific Research at the University of Jordan, Amman, Jordan, in accordance with the criteria established in the Declaration of Helsinki (2013 revision). Furthermore, permission was obtained from the Institutional Review Board (IRB) of the Autism Academy of Jordan (IRB No.: 19/192, Date: March 25, 2019). Informed written consent was obtained from the parents or guardians of all children participating in the study before its initiation.

Behavioral Assessment

Behavioral outcomes were evaluated with the Assessment of Basic Language and Learning Skills-Revised (ABLLS-R) approach, administered by a qualified special education professional. Assessments were conducted at baseline (week 0) and thereafter following the conclusion of the supplementation period (week 6). The ABLLS-R approach includes observation across 25 ability domains, such as language, social interaction, self-help, academic abilities, and motor functions[46, 47].

Sublingual L-Glutathione Supplementation

Participants received sublingual L-glutathione tablets (Clinical Glutathione™, Europharma®, France), each containing 300 mg of reduced glutathione, administered twice daily (morning and evening) for a total daily dose of 600 mg over a continuous 6-week period. The tablets were sugar-free and free from gluten and artificial preservatives, containing maltitol, hydroxypropylmethylcellulose, vanilla flavor, pomegranate extract, and vegetable-derived magnesium[41].

A clinical pharmacist on the study team was responsible for providing the glutathione tablets and educating caregivers on how to use them correctly, including placing the tablet under the tongue until fully dissolved. The pharmacist also provided tips to support adherence and followed up regularly with families to monitor use, address any side effects or difficulties, and ensure safe and consistent dosing throughout the study. This involvement helped improve compliance and supported the effective delivery of the therapy.

Biochemical Analysis

Chemicals and Reagents

All biochemical assay kits were procured from MyBioSource (USA), including hTOS, human GSSG, human GSH, and human MDA enzyme-linked immunosorbent assay (ELISA) kits, ; Glutathione assay kit, TAC, microplate assay kit, and protein carbonyl colorimetric assay kit. Clinical Glutathione™ Patented, Reduced Oral Glutathione (300 mg) was obtained from Terry Naturally, Europharma® (France). Analytical grade chemicals and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Study Population and Sample Collection

Serum samples were collected from individuals with autism and control subjects using a standardized protocol. Blood samples were drawn in the morning after an overnight fast, processed within 2 hours of collection, and serum was separated by centrifugation at 3000 rpm for 10 minutes at 4°C. Serum samples were stored at -80°C in aliquots to avoid repeated freeze-thaw cycles until analysis.

Measurement of Glutathione (GSH) Levels in Human Serum

Serum glutathione concentrations were quantified using a

competitive enzyme-linked immunosorbent assay (ELISA) designed for quantitative analysis of GSH in biological samples[48]. The procedure involved adding 100 µL of undiluted serum to microplate wells previously coated with a monoclonal antibody specific to GSH. Following the addition of the sample, 100 µL of horseradish peroxidase (HRP)-linked detection antibody was added to each well.

The microplate was incubated at 37°C for 60 minutes to allow antibody-antigen binding. After incubation, unbound components were removed through thorough washing with phosphate-buffered saline containing 0.05% Tween 20. Color development was initiated by adding 50 µL each of chromogen solutions A and B to the wells, followed by 15 minutes of incubation in the dark.

The enzymatic reaction was terminated by adding 50 µL of stop solution, which changed the solution color from blue to yellow. Optical density (OD) was measured at 450 nm using an automated ELISA reader (AccuReader version 1.10).

GSH concentrations were determined by constructing a standard curve from known GSH concentrations, with sample concentrations interpolated from this curve using linear regression analysis[35]. All samples were analyzed in duplicate, and the coefficient of variation for replicate measurements was less than 5%.

Quantification of Oxidized Glutathione (GSSG)

GSSG levels in diluted human serum samples were quantified using a competitive enzyme immunoassay method. Serum samples were diluted at a ratio of 1:5 using the supplied sample diluent. In this test, 50 µL of diluted sample and 50 µL of GSSG-HRP conjugate were introduced to wells that pre-coated with an anti-GSSG antibody. The plate was incubated at 37°C for one hour. Following incubation, the wells were rinsed to remove any unattached compounds. Fifty microliters of chromogen solutions A and B were subsequently added and incubated in the dark for 15 minutes[35,49]. The reaction was terminated by the addition of 50 µL of stop solution, and the optical density was measured at 450 nm. A standard curve was established, and GSSG values in the samples were interpolated accordingly. In competitive ELISA formats, the optical density (OD) is inversely related to the concentration of GSSG in the sample.

Glutathione Redox Ratio (GSH/GSSG) Calculation

The redox status of glutathione was assessed by calculating the ratio of GSH to GSSG (GSH/GSSG) for each sample, providing insight into the oxidative balance within the serum.

Determination of Malondialdehyde (MDA) Levels

Serum MDA levels were quantified with a double-sandwich ELISA methodology. This procedure involved pre-coating wells with a monoclonal antibody specific to human MDA. One hundred microliters of serum samples were added to the wells, followed by the addition of 100 microliters of biotin-labeled detection antibody. The plate was incubated at 37°C for one hour. Following washing to eliminate unbound antibodies, 100 µL of avidin-peroxidase conjugate was added to each well and incubated for 30 minutes at 37°C. Subsequent to a washing step, 90 µL of substrate solution was introduced and incubated in the absence of light for 15 minutes to facilitate color development[50]. The reaction was concluded by the addition of 50 µL of stop solution, and the optical density was assessed at 450 nm. A standard curve was constructed, and MDA concentrations in the samples were derived from this curve.

Evaluation of Total Oxidant Status (TOS)

TOS was assessed in unadulterated human serum samples with a colorimetric technique. In this test, the oxidants in the sample oxidize the ferrous ion–chelator complex to ferric ion[51]. The ferric ion creates a colorful complex with a chromogen in an acidic environment. For each sample, 75 µL of reagent 1 (chromogen solution) was added to the wells, followed by the addition of 5 µL of serum sample and 11 µL of reagent 2 (ferrous ion solution). The plate was incubated at 37°C, and the absorbance was measured at 530 nm at three intervals: 30 seconds, 5 minutes, and 10 minutes. The variation in absorbance (ΔAbs) was computed, and the total quantity of oxidant molecules in the sample was ascertained using the subsequent equation:

TOS (µmol H2O2 equiv./L) = Standard Abs × ΔAbs × Standard Concentration,

where ΔAbs represents the change in absorbance of the sample, Standard Abs denotes the absorbance change of the standard solution, and Standard Concentration indicates the concentration of the standard solution.

Total Antioxidant Capacity (TAC) Measurement

Serum TAC was quantified using a colorimetric method based on the reduction of Fe^{3+}-TPTZ complex to Fe^{2+}-TPTZ. Serum samples were first diluted 1:10 with the supplied diluent.

The assay procedure involved adding 100 µL of acetate buffer (reagent 1) to each well of a microplate, followed by 10 µL of diluted serum sample and 100 µL of Fe^{3+}-TPTZ complex solution (reagent 2). The plate was incubated at 37°C for 10 minutes to allow the antioxidant-mediated reduction reaction to occur, resulting in the formation of a blue-colored Fe^{2+}-TPTZ complex[52]. Absorbance was measured at 593 nm using an automated ELISA reader (AccuReader version 1.10). A calibration curve was generated using Trolox standards (6-1500 µmol/L) to quantify the antioxidant capacity of serum samples. The TAC values were expressed as Trolox equivalents (µmol/L) based on the linear regression analysis of the standard curve. All samples were analyzed in triplicate to ensure measurement precision.

Protein Carbonyl Content Analysis

Protein carbonyl content was measured using a colorimetric assay based on the reaction with 2,4-dinitrophenylhydrazine (DNPH). Briefly, serum samples were incubated with DNPH reagent for 15 minutes at room temperature, followed by the addition of a stop solution. The resulting hydrazone derivatives were then reacted with a colorimetric detection reagent, and the absorbance was measured at 370 nm. The protein carbonyl

content was calculated using a standard curve generated with known concentrations of carbonyl standards[53]. Samples not analyzed immediately were stored at -70°C for up to one month to maintain stability.

Assay Validation and Standardization

To ensure analytical reproducibility, all biochemical assays were conducted in triplicate, with acceptable precision defined as coefficient of variation (CV) values less than 10%. For each assay run, standard curves were prepared using manufacturer-supplied calibration standards, and sample concentrations were determined through linear interpolation from these calibration curves.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 7.04. Data were presented as mean ± standard deviation (SD). Differences in biochemical parameters before and after supplementation were assessed using One-Way ANOVA, with statistical significance set at $P < 0.05$. Behavioral outcomes were analyzed using independent t-tests, with a threshold of $P < 0.05$ considered statistically significant.

RESULTS

Effect of glutathione supplementation on oxidative stress in ASD individuals

The physiological impacts of glutathione supplementation on oxidative stress indicators in autistic and normal children (control group) are illustrated in Table 1 and Figure 1. Table 1 presents a comparative examination of blood antioxidant efficacy markers between autistic group (n=25) and control group (n=25) at baseline then after 3 and 6 weeks of glutathione supplementation.

The data illustrates the temporal changes in antioxidant status and oxidative stress parameters. At baseline, autistic children exhibited significantly lower serum GSH levels (2.84 ± 0.86 µmol/l vs. 8.69 ±1.48 µmol/l in controls, p<0.05), reflecting an impaired reduced glutathione status. Conversely, oxidized glutathione (GSSG) levels were elevated in autistic children (0.56 ± 0.08 µmol/l vs. 0.25 ± 0.06 µmol/l in controls, p<0.05), resulting in a markedly reduced GSH/GSSG ratio (5.23 ± 1.77 vs. 29.51 ± 3.92 in controls, p<0.05). TAC markers were also lower in autistic children (0.49 ± 0.09 mmol/l vs. 1.36 ± 0.06 mmol/l in controls, p<0.05), In contracts oxidative stress markers, including total oxidant status (TOS, 47.48 ± 1.46), malondialdehyde (MDA, 2.09 ± 0.44), and carbonyl proteins (1.25 ± 0.17 µmol/l) were significantly higher compared to controls (p<0.05 for all)

After 3 weeks of supplementation, autistic children showed a modest increase in serum GSH (3.29 ± 0.39 µmol/l, p<0.05 vs. baseline) and a slight improvement in the GSH/GSSG ratio (5.77 ± 0.71, p<0.05 vs. baseline). However, values remained significantly lower than those controls. GSSG levels decreased non- significantly (0.54 ± 0.05 µmol/l). TAC increased minimally (0.50 ± 0.06 mmol/l, p<0.05 vs. baseline) but remained below control levels (Table 1 and Figure 1). Oxidative stress markers (TOS, MDA, carbonyl proteins) showed a slight improvement compared to the baseline, with no statistically significant changes.

By 6 weeks, GSH levels in autistic children had further increased significantly comparing to baseline, and the GSH/GSSG ratio also significantly improved comparing to baseline to 6.19 ± 0.22, however, both remained significantly lower than controls (p<0.05). TAC rose to 0.57 ± 0.06 mmol/l (p<0.05 vs. baseline), though still below control values. Also, TOS and MDA levels were significantly decreased in autistic children as compared to baseline (TOS: 46.17 ± 0.78 µmol H_2O_2 Equiv./l; MDA: 1.76 ± 0.16 µmol/l;). Notably, carbonyl proteins (1.25 ± 0.07 µmol/l) persisted at elevated level compared to controls (p>0.05), with no significant; supplementation-induced reductions observed.

Control children maintained stable antioxidant and oxidative stress parameters throughout the study, with no significant changes in GSH, GSSG, TAC, TOS, MDA, or carbonyl proteins across time points (p>0.05 for all comparisons).

The impact of sublingual glutathione supplementation on behavioral outcomes in subjects with ASD.

The impact of sublingual glutathione supplementation on behavioral outcomes in individuals with autism was assessed using the Assessment of Basic Language and Learning Skills-Revised (ABLLS-R) system, with results presented in Table 2.

Table 1. Comparison of serum antioxidant efficacy status between autistic and control children before and after reduced glutathione supplementation.

	Baseline		After 3 weeks		After 6 weeks	
	ASD	**Control**	**ASD**	**Control**	**ASD**	**Control**
GSH (µmol/l)	2.84± 0.86	8.67±1.5	3.29± 0.39	8.72±1.35	3.816 ± 0.37	8.66±1.76
GSSG (µmol/l)	0.56 ± 0.08	0.25±0.058	0.54± 0.051	0.25±0.06	0.47 ± 0.05	0.25±0.07
GSH/GSSG (µmol/l)	5.23 ± 1.77	29.51±3.92	5.77 ± 0.71	28.87±2.54	6.19 ± 0.22	30.02±3.5
TAC (mmol/l)	0.49±0.09	1.36±0.058	0.50± 0.06	1.32±0.07	0.572 ± 0.06	1.42±0.06
TOS (µmol H2O2 Equiv./l)	47.48±1.46	42.800±3.14	46.71± 0.48	41.94±1.21	46.17± 0.78	43.02±2.12
MDA (µmol/l)	2.09 ± 0.44	0.82±0.20	1.94 ± 0.09	0.78±0.32	1.76 ± 0.16	0.84±0.33
Carbonyl proteins (µmol/l)	1.25± 0.17	0.83±0.10	1.25±0.14	0.78±0.12	1.25±0.07	0.87±0.05

GSH-Reduced glutathione, GSSG-Oxidized glutathione, TAC-Total antioxidant capacity, TOS-Total oxidant status, MDA-Malondialdehyde. Results were expressed as means of 25 measures ± SD (autistic n=25, control n=25) and were analyzed using t-test p<0.05.

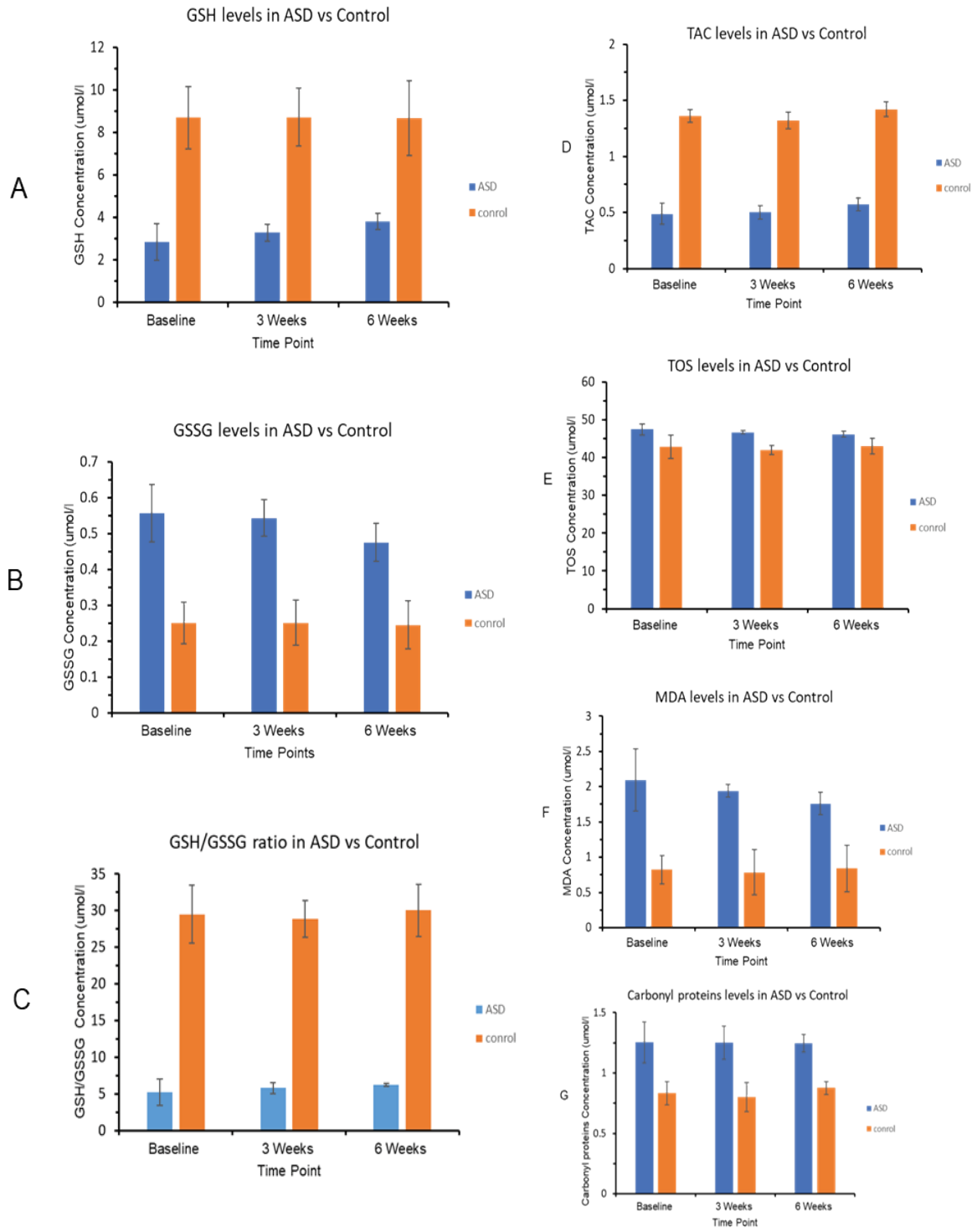

Figure 1. Bar charts showing the mean ± standard deviation of several oxidative stress and antioxidant markers in individuals with autism spectrum disorder (ASD) compared with control subjects, measured at three-timepoints (baseline, 3 weeks, and 6 weeks). (A) Reduced glutathione. (B) Oxidized glutathione. (C) GSH/GSSG ratio. (D) Total antioxidant capacity (TAC). (E) Total oxidative status (TOS). (F) Malondialdehyde (MDA, µmol/l). (G) Carbonyl proteins. The blue bars represent the ASD group, and orange bars represent the control group.

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Table 2. The behavioral analysis of the autistic individuals using the ABLLS-R system before and after the glutathione supplementation.

Parameter	Range	Before supplementation (week 0)	After supplementation (week 6)
The Behavioral		**Mean ± SD**	**Mean ± SD**
Cooperation and reinforce effectiveness	1-19	12.6 ± 5.52	14.7 ± 4.76 *
Imitation	1-27	18.12 ± 9.08	21.28 ± 6.66*
Play and Leisure	1-15	5.64 ± 2.46	9.2 ± 3.122 *
Social interaction	1-34	6.32 ± 3.25	10.2 ± 4.33 *
Group Instruction	1-12	5.2 ± 2.483	5.2 ± 2.47
Classroom Routines	1-10	5.52 ± 2.93	5.52± 2.93
Generalized Responding	1-6	2.32± 2.34	2.32± 2.34
Reading	1-17	0.28±0.891	0.28±0.89
Math	1-29	0.12± 0.6	0.12±0.6
Spelling	1-7	0.00±0.000	0.00±0.000
The Occupational			
Writing	1-10	2.64± 2.53	2.64± 2.53
Visual Performance	1-27	2.24±2.126	5.44±3.37 *
Dressing	1-15	8.16± 4.64	8.16± 4.64
Eating	1-10	6.00 ± 3.149	6.00± 3.149
Grooming	1-7	3.88± 2.33	3.88± 2.33
Toileting	1-10	5.76±3.455	5.76± 3.455
Gross motor	1-30	9.44± 7.91	9.44± 7.91
Fine motor	1-28	14.44± 8.31	14.44± 8.31
Speech and Language			
Requests	1-29	5.88± 4.176	5.88± 4.176
Vocal imitation	1-20	6.52± 6.42	9.76± 6.45 *
Spontaneous Vocalizations	1-9	2.24± 4.03	2.24± 4.03
Syntax grammar	1-20	0.24± 0.597	0.24± 0.597
Labeling	1-47	2.04± 3.69	2.04± 3.69
Receptive Language	1-57	15.76± 8.49	19.24± 9.14 *
Intraverbals	1-49	1.44± 1.386	1.44± 1.386

* Significant. SD-Standard deviation**.** Results were expressed as means of 25 measures ± SD and were analyzed using t-test p<0.05.

Behavioral evaluations were conducted at baseline and after six weeks of supplementation, examining improvements across three primary domains: behavioral, occupational, and speech and language.

In the behavioral domain, significant improvements were observed post-supplementation in several parameters. Specifically, the mean scores for cooperation and reinforcement effectiveness significantly increased from 12.6 ± 5.5 at baseline to 14.7 ± 4.7 after six weeks. Similarly, significant improvements were recorded in imitation (baseline: 18.12 ± 9.08; after supplementation: 21.28 ± 6.66), play and leisure (baseline: 5.64 ± 2.46; after supplementation: 9.2 ± 3.122), and social interaction (baseline: 6.32 ± 3.25; after supplementation: 10.2 ± 4.33). Other parameters within this domain, such as group instruction, classroom routines, generalized responding, reading, math, and spelling, did not demonstrate significant changes following glutathione supplementation (p>0.05).

Within the occupational domain, a statistically significant enhancement was documented solely for visual performance, with scores improving from 2.24 ± 2.126 at baseline to 5.44 ± 3.37 after the supplementation period (p=0.0002). Other assessed parameters, including writing, dressing, eating, grooming, toileting, gross motor, and fine motor skills, showed no statistically significant differences post-intervention (p>0.05).

In the speech and language domain, glutathione supplementation led to notable improvements in vocal imitation (baseline: 6.52 ± 6.42; after supplementation: 9.76 ± 6.45; p=0.0019) and receptive language (baseline: 15.76 ± 8.49; after supplementation: 19.24 ± 9.14; p=0.0038). In contrast, no significant changes were observed in parameters such as requests, spontaneous vocalizations, syntax and grammar, labeling, and intraverbals (p>0.05).

Collectively, these findings highlight selective yet significant

improvements in specific behavioral, occupational, and communicative functions following six weeks of sublingual glutathione supplementation in individuals with ASD.

DISCUSSION

Clinical evidence indicates that oral glutathione supplementation and alternative approaches to elevate glutathione levels might significantly enhance antioxidant indicators in children with ASD, potentially restoring elements of their redox status[37]. Nonetheless, the effect of these therapies on ASD symptoms remains inconsistent and significantly vary among studies[37,40]. The heterogeneity in clinical outcomes may be attributed, at least partially, to variances in the oral bioavailability of glutathione, which is often restricted and exhibits considerable inter-individual variation. The sublingual administration of glutathione may offer a viable solution, perhaps overcoming challenges associated with inadequate or variable gastrointestinal absorption. Thus, boosting antioxidant equilibrium using refined glutathione administration techniques may alleviate oxidative stress-related neuronal injury, thereby improving behavioral results in patients with ASD[37,40]. This study investigated the biochemical and behavioral effects of sublingual glutathione supplementation in a pediatric population diagnosed with ASD. To our knowledge this study is one of the first to simultaneously assess oxidative biomarkers and behavioral responses to sublingual glutathione delivery in children with autism.

Our findings revealed significant biochemical abnormalities indicative of elevated oxidative stress in autistic children compared to matched healthy controls at baseline, including lower serum concentrations of reduced glutathione (GSH) and total antioxidant capacity (TAC), alongside elevated levels of oxidized glutathione (GSSG), total oxidant status (TOS), malondialdehyde (MDA), and carbonyl proteins. These results align with prior studies reporting increased oxidative stress and impaired antioxidant defenses in autistic populations[36,54]. Such biochemical imbalances have been hypothesized to contribute to the neuropathology associated with ASD, particularly affecting cognitive, behavioral, and communicative functions through neuronal oxidative damage and mitochondrial dysfunction[42].

Our biochemical findings demonstrated that six weeks of sublingual glutathione supplementation significantly improved antioxidant profiles in autistic subjects, indicated by marked elevations in serum GSH levels and the GSH/GSSG ratio, alongside reductions in serum GSSG, TOS, and MDA concentrations. Notably, these changes were progressive, with greater improvements observed after 6 weeks compared to the intermediate measurement at three weeks. These outcomes demonstrate the effectiveness of sublingual glutathione in augmenting systemic antioxidant defenses and reducing oxidative damage. The minimal improvement after three weeks, followed by a more pronounced effect after six weeks, suggests a cumulative and time-dependent response to supplementation.

Importantly, the improved bioavailability and efficacy observed with sublingual glutathione supplementation might be attributed to the avoidance of gastrointestinal degradation by γ-glutamyl transpeptidase (GGT), an enzyme responsible for the poor oral bioavailability of glutathione[55,56]. Previous comparative studies by Kern et al. (2011)[37] found only slight improvements with oral glutathione administration and no significant improvements with transdermal application. Our results are consistent with these findings, further reinforcing the advantages of sublingual administration as an efficient and practical method for elevating GSH levels.

The positive outcomes of sublingual glutathione therapy in children with ASD highlight the expanding role of pharmacists, particularly as part of the research team, in supporting antioxidant-based interventions in autism care. Given the high prevalence of oxidative stress in ASD, proper administration, consistent adherence, and caregiver education are critical to the success of such therapies. Clear guidance on the safe and effective use of supplements like glutathione can significantly improve treatment outcomes. Tools like visual medication schedules and ongoing follow-up help ensure correct dosing and allow early identification of potential issues. By integrating antioxidant therapy with standard treatment plans and considering individual metabolic needs and possible interactions, care becomes more comprehensive and patient-centered, ultimately enhancing the quality of life for children with ASD.

Behavioral improvements subsequent to glutathione supplementation were evaluated utilizing the Assessment of Basic Language and Learning Skills-Revised (ABLLS-R) system, a recognized and thorough instrument employed for assessing communication, social interaction, adaptive behavior, and learning competencies in individuals with ASD[13,47]. The ABLLS-R system enables comprehensive profiling across several domains, such as behavioral, occupational, and speech and language parameters, and is essential for monitoring developmental progress and directing personalized therapy interventions[46]. Our study utilized this comprehensive assessment method to record substantial improvements in cooperation, reinforcement efficacy, imitation abilities, play and leisure activities, social interactions, visual performance, vocal imitation, and receptive language. The focused enhancements highlight the potential benefits of sublingual glutathione supplementation, suggesting a favorable correlation between enhanced antioxidant levels and improved functional behavioral outcomes in children with ASD.

However, not all measured behavioral parameters showed improvement, underscoring that the benefits of glutathione supplementation may target specific behavioral deficits rather than providing universal improvements across all assessed areas. This selective improvement aligns with previous studies exploring antioxidants in ASD, where some interventions demonstrated efficacy on certain symptoms without affecting others[57,58]. For instance, vocal imitation and receptive language improved significantly in our study, whereas parameters such as syntax and grammar, as well as spontaneous vocalizations,

remained unaffected. The selective nature of these improvements may reflect differences in underlying neural mechanisms responsive to oxidative stress modulation.

In comparing our findings with those of other antioxidant interventions, it is notable that while some antioxidant supplements, such as methyl B12 and omega-3 fatty acids, demonstrated limited or no significant clinical improvement in core autism symptoms[57,58], our sublingual glutathione supplementation exhibited clearer biochemical and targeted behavioral benefits. These differential outcomes highlight the potentially unique role that glutathione may play in mitigating oxidative stress and improving core autism-related behavioral deficits, particularly in receptive language, imitation, social interactions, and cooperative behaviors.

Despite promising outcomes, the current study has limitations. The relatively small sample size and short-term intervention duration limit the generalizability of results. Additionally, the open-label, pre-post design precludes exclusion of placebo effects. Therefore, future studies should consider larger randomized controlled trials, longer intervention durations, and the use of placebo-controlled designs to further validate these preliminary findings.

CONCLUSION

In conclusion, our study highlights the potential benefits of sublingual glutathione supplementation in enhancing serum antioxidant status and improving specific behavioral outcomes in children with ASD. These findings provide valuable evidence supporting the therapeutic utility of antioxidant supplementation strategies in the management of ASD. The involvement of pharmacists in counseling, adherence support, and monitoring contributed to the safe and effective delivery of therapy. Future studies should focus on longitudinal effects, identify responders through biomarkers, and clarify optimal dosage regimens to refine further the clinical application of glutathione supplementation in ASD treatment

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors used QuillBot and ChatGPT to improve the language and readability of the manuscript. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools

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