

Breaking the cycle of oxidative stress for better behavioral health in autism spectrum disorder: A scoping review

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ABSTRACT

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition marked by socio-communicative and behavioral challenges. ASD is increasingly linked to oxidative stress, which stems from a destructive imbalance state whereby excessive reactive oxygen species (ROS) overwhelm antioxidant defenses. This redox imbalance triggers a cascade of cellular dysfunctions, which in neurons include synaptic inefficiency, altered receptor function, excitotoxicity, and chronic neuroinflammation. All these dysfunctions add an additional burden to the genetic and epigenetic contributions underlying autism pathophysiology in each single individual, ultimately exacerbating ASD core symptoms. Strikingly, children with ASD exhibit diminished antioxidant capacity, correlated with heightened behavioral severity and impaired quality of life. This scoping review explores the intricate relationship between oxidative stress and ASD, evaluating current therapeutic strategies aimed at restoring redox balance while identifying critical research gaps. Interventions such as N-acetylcysteine (NAC), vitamin and mineral supplementation, and dietary antioxidants have shown promise in mitigating oxidative damage and improving social responsiveness. Other strategies, in particular hyperbaric oxygen therapy (HBOT) and cleanroom environments, are highly controversial. Well-designed randomized placebo-controlled trials (RCTs) integrating clinical and psychodiagnostic measures with precision medicine frameworks, are crucial for developing targeted therapies that, restoring redox homeostasis, may optimize neurodevelopmental outcomes. By summarizing current evidence and addressing these gaps, this review underscores the therapeutic potential of oxidative stress correction in improving the quality of life of individuals with ASD.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition impacting all aspects of life, including behavior, self-care, and complex

social functioning (Aishworiya et al., 2022; Kereszturi, 2023; Maenner et al., 2023; Tafolla et al., 2025), and its prevalence has shown a notable increase in recent years (Talantseva et al., 2023). The severity of clinical symptoms correlates with increased aberrant behaviors (Suvannang

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et al., 2024), which further impede learning, socialization and overall well-being (Harris and Coyle, 2022; Simonoff et al., 2008). This exacerbates the complexity and difficulty of treatment (Aishworiya et al., 2022). Various factors contribute to ASD etiology, including genetic variants, environmental influences, and immune dysreactivity both prenatally and early postnatally (Kereszturi, 2023; Lord et al., 2018; Wang et al., 2023). The extreme interindividual heterogeneity and all these complexities result in intervention strategies which vary significantly from patient to patient and across the world.

The clinical management of ASD symptoms and aberrant behaviors in children with ASD is generally based on behavioral intervention, different forms of psychotherapy, and pharmacotherapy (Persico et al., 2021). However, these interventions often yield suboptimal results due to the time-intensive nature and high costs of behavioral interventions, and to the potential side effects associated with pharmacological treatments (Aishworiya et al., 2022; Cucinotta et al., 2022; Doyle and McDougle, 2012). Emerging evidence suggests that oxidative stress plays a significant role in the pathophysiology of ASD. This relationship is not age-dependent but involves chronic inflammatory responses, DNA and protein damage, and mitochondrial superoxide production, all of which exacerbate dysfunction in individuals with ASD (Chauhan and Chauhan, 2006).

Oxidative stress impacts neuronal function by reducing membrane fluidity, impairing nerve synapse efficiency (particularly in long-distance connectivity critical for information integration), disrupting receptor function, and even inducing cell death. It also affects neuronal development, immune dysregulation and neuroinflammation, energy production, prostaglandin synthesis, and excitotoxicity (Palmieri and Persico, 2010). Insufficient antioxidant capacity, unable to neutralize and eliminate oxidants, has been linked to more severe clinical symptoms and aberrant behaviors in children with ASD (Usui et al., 2023). Thus, efforts to control oxidative stress may be worthwhile, to improve behavioral symptoms and neuropsychological deficits in patients with ASD (Cucinotta et al., 2022). Moreover, efforts to enhance antioxidant capacity through supplementation offer a promising strategy for mitigating symptoms and improving quality of life (Usui, Kobayashi, and Shimada, 2023), while personalized, genetic-based pharmacological therapies can be provided only to few patients (Butler et al., 2022) and critical periods in development pose a formidable age limit to the efficacy of all interventions (Starkey et al., 2023).

Several non-enzymatic antioxidants, such as vitamin E and vitamin C, folic acid, cobalamin (vitamin B12), vitamin B6, vitamin D, zinc, and iron, function to strengthen the activity of enzymatic antioxidants in the reduction-oxidation cycle that occurs in the brain (Adams et al., 2022; Pangrazzi, Balasco, and Bozzi, 2020; Rossignol and Frye, 2021). Additionally, several nutraceuticals display therapeutic potential for ASD (Sachdeva et al., 2022; Persico et al., 2025).

Despite the growing body of research on oxidative stress in ASD, most currently available reports focus on the general link between oxidative stress and ASD or on specific antioxidants (Kuźniar-Palka, 2025). This scoping review seeks to provide a novel, comprehensive exploration of therapeutic strategies targeting oxidative stress to improve behavioral symptoms in ASD. By integrating findings from pharmacological, nutraceutical, non-pharmacological, and lifestyle interventions, this review highlights innovative approaches and identifies gaps in current research. This study also aims to emphasize the potential offered by tailored strategies based on individual oxidative stress profiles and their impact on behavioral outcomes.

2. Material and methods

2.1. Search strategy

The central research question addressed in this study is the following: What is the impact of therapeutic interventions aimed at reducing oxidative stress on behavioral symptoms in individuals with

ASD? In this scoping review, the authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines to identify relevant studies (Tricco et al., 2018). The search strategy employed the following keywords: "(autism OR autism spectrum disorder OR asd) AND (oxidative stress) AND (therapy OR treatment OR antioxidants)", targeting titles or abstracts of studies. The search was conducted across five databases: PubMed, MDPI, Springer Link, Science Direct, and EBSCO host with publications date up to May 2025. A detailed list of the keywords used in each database is provided in [Supplementary Table S1](#). The final protocol for this scoping review was prospectively registered with the Open Science Framework (OSF) under DOI <https://doi.org/10.17605/OSF.IO/VQPDJ>. Although our protocol registered in OSF initially specified the literature search to end in March 2025, we extended the search up to May 2025 to ensure inclusion of the most recent studies.

2.2. Eligibility criteria

2.2.1. Participant & concept

This scoping review includes studies focusing on therapeutic strategies to improve behavioral or altering oxidative stress markers in human subjects with ASD.

2.2.2. Type of sources

Eligible sources include any study performed on human samples (i.e. randomized controlled trials, cohort studies, case-control studies, cross-sectional studies) published up to May 2025. Reviews (i.e. systematic review, literature review), letters to the editor, single case reports and articles not written in English, French, or Italian were excluded.

2.3. Search terms

Literature was searched by identifying studies with term "(autism OR autism spectrum disorder OR asd) AND (oxidative stress) AND (therapy OR treatment OR antioxidants)". The final search results were exported into Mendeley, and duplicates were removed.

2.4. Study selection

After duplicates were removed, articles retrieved from each database were selected by two reviewers who independently screened titles and abstracts. During this step, titles not relevant or not fitting our inclusion criteria (i.e. review articles, animal and laboratory studies, and opinion articles) were removed. Then, article with available full-texts were reviewed, based on eligibility criteria.

2.5. Data extraction and analysis

A data-charting form was collaboratively created by the two reviewers, to identify which variables to extract. Ultimately, the following variables were extracted from each study: medication, authors and year of publication, study design, duration, sample size, age (yr), mean dose, outcome measures, therapeutic effects, and side effect reported in the treated group. The two reviewers independently recorded the data, discussed their findings, and continuously refined the data-charting form through an iterative process by categorizing the data into natural treatments, vitamins & minerals, coenzymes/antioxidants, probiotics, other supplements, pharmacotherapy, and intervention therapies.

The main outcomes of interest for this review were: (1) To identify the impact of various interventions to reduce oxidative stress and to improve behavioral symptoms in ASD; and (2) To assess the effect of enhancing total antioxidant capacity on aberrant behaviors in ASD.

3. Results and discussion

The PRISMA flow chart of this review is shown in [Fig. 1](#). Our

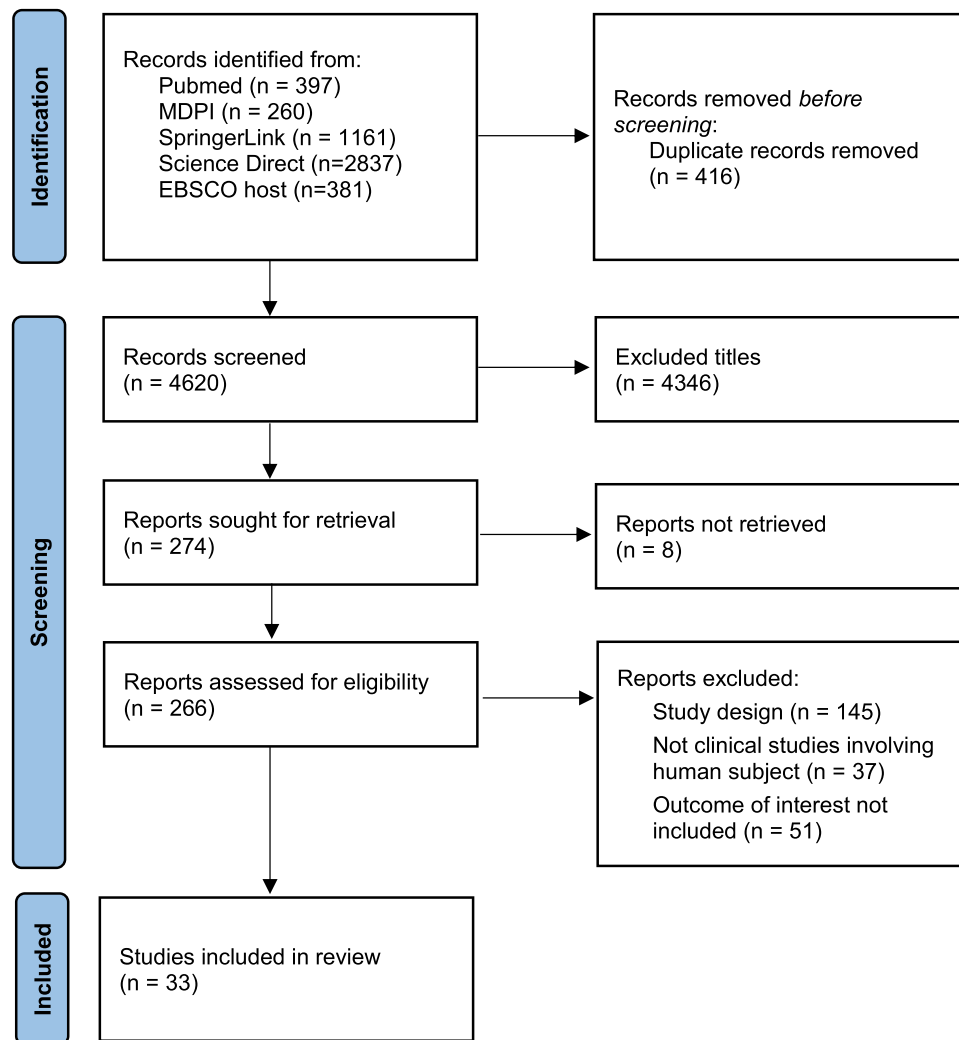


Fig. 1. PRISMA Flowchart.

electronic literature search retrieved 5036 articles. Four hundred sixteen studies were eliminated for duplication, and 4346 articles were excluded by title screening. After abstract reading, 233 additional articles were excluded (145 articles due to study design, 37 were not clinical studies involving human subjects, and 51 did not include the outcome measures of interest for this review). Among the remaining 41 articles, 8 did not provide access to the full text, ultimately leaving 33 studies to be included in the present review. The summary of these 33 studies is presented in Table 1.

In reference to study design, the majority of studies consists in 20 (61 %) randomized controlled trials (RCTs), followed by 10 (30 %) clinical trials, 1 (3 %) observational studies, 1 (3 %) cross-sectional studies and 1 (3 %) case studies. Sample sizes are generally small-to-medium, ranging from 7 to 141 patients (mean = 44.3), with 10/33 (30.3 %) studies involving less than 30 cases (Table 1). Samples also appear heterogeneous in reference to ASD severity.

The Literature encompasses a range of therapeutic interventions for ASD spanning highly diverse approaches, including nutraceutical, pharmacological, and non-conventional therapies.

3.1. Vitamins and minerals

Vitamins and minerals offer promising benefits for both metabolic and behavioral symptoms in ASD, particularly by addressing oxidative stress, methylation, and mitochondrial dysfunction. Folic acid has

been associated with improvements in communication and behavior, with Batebi et al. (2020) reporting reduced hyperactivity and irritability at higher doses, while Sun et al. (2016) observed enhanced sociability and language with lower doses, alongside better glutathione redox balance. Methylcobalamin (B12), alone or with folic acid, has also been shown to boost glutathione and improve behavior (James et al., 2009; Corejová et al., 2022), though effects may be subgroup-specific (Bertoglio et al., 2010). Hendren et al. (2016) linked clinical improvement measures to increased methionine, reduced SAH, and a better SAM/SAH ratio. These effects align with underlying metabolic issues in ASD, including impaired methylation and oxidative stress, which disrupt methionine and SAM levels and elevate homocysteine (Muratore et al., 2013). Addressing these imbalances through targeted nutrition may at least partly exert positive effects also on core ASD symptoms. Broad-spectrum supplementation supports this approach: Adams et al. (2011) found that a multivitamin formula improved metabolic markers and behaviors, while Hill et al. (2025) reported gains in socialization and communication using mitochondrial-targeted supplements. Similarly, Cucinotta et al. (2022) and Persico et al. (2023) found that a regimen combining vitamins E, B-complex, and Q10 ubiquinol improved cognition and social motivation in children with ASD and related disorders (Phelan-McDermid Syndrome). While the benefits are significant, side effects in all of these studies are generally mild and transient, such as gastrointestinal issues, increased appetite, and mild behavioral changes, with no serious adverse events reported.

Table 1

Summary of the included studies.

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
Vitamins and minerals								
Folinic acid	Batebi et al., (2020)	RCT, 10 weeks	55	4–12	2 mg/kg up to 50 mg per day	ABC-C, ESRS	Improvement: folinic acid.>placebo in ABC-C score for inappropriate speech, stereotypic behavior, hyperactivity/ compliance, and irritability No difference in lethargy/social withdrawal subscale score. Time×treatment interaction for inappropriate speech, stereotypic behavior, and hyperactivity subscale scores; no effect for lethargy/ social withdrawal and irritability.	Dizziness (4), Sedation (3), Abdominal pain (4), Increased appetite (7), Headache (1), Diarrhea (5), Constipation (4), Rash (1)
Folinic acid	Sun et al., (2016)	Clinical Trial, 3 months	66	3.5–6	400 µg two times daily	ABC, CARS, ATEC, and PEP–3, Vit B12, folic acid, homocysteine, and glutathione	Improved sociability, cognitive verbal/ preverbal abilities, receptive language, and emotional expression and communication. Increased concentrations of folic acid, reduced homocysteine, and normalized glutathione redox metabolism. No change in vitamin B12 concentrations.	No side effects reported in this study.
Methyl B12 & folinic acid	James et al., (2009)	RCT, 3 months	40	2–7	Methyl B12 75 µg/kg (twice/wk) and folinic acid 400 µg (twice/day)	SAM, SAH cysteine, cysteinylglycine, glutathione plasma concentrations	No change in methionine, SAM, or SAH concentrations. Significant increase in cysteine, cysteinylglycine, and glutathione levels ($P < 0.001$). Additionally, the oxidized disulfide form of glutathione decreased, while the glutathione redox ratio increased following treatment ($P < 0.008$).	Mild hyperactivity (4), awakenings (1), difficulty falling asleep (1), impulsiveness (1), irritability (1).
Methyl B12	Corejová et al., (2022)	RCT, 200 days	25	4–20	500 µg/5 mL per day	Clinical and psychological status evaluated by parents and psychologist; plasma vitamin B12, homocysteine, and cysteine reduced/ oxidized glutathione (GSH/GSSG).	Methylcobalamin treatment gradually improved overall clinical and psychological status, with the greatest impact observed in the social domain, followed by cognitive, behavioral, and communication aspects. These improvements were strongly associated with increases in reduced glutathione levels and the enhanced reduced-to-oxidized glutathione ratio.	Sleep disorders (5), emotional dysregulation (4), hyperactivity (6), licking or putting in mouth inappropriate objects (3).
Methyl B12	Hendren et al., (2016)	RCT, 8 weeks	57	3–7	75 µg/kg every 3 days	CGI-I, parent-rated ABC or SRS. Methionine, SAM,	Significant improvement in CGI-I score with methyl B12	No significant difference in frequency of adverse

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
						SAH plasma concentrations	compared to placebo ($p = 0.005$). Clinical improvement is correlated with increased plasma methionine ($p = 0.05$), decreased SAH ($p = 0.007$), and improved SAM/SAH ratio ($p = 0.007$), suggesting enhanced cellular methylation capacity. No change in parent-rated ABC or SRS.	events (cold, fever, flu, hyperactivity, irritability, insomnia, attention deficit, mouthing, nosebleed, rash, stomach flu).
Methyl B12	Bertoglio et al., (2010)	Pilot study, RCT, 12 weeks	30	3–8	64.5 µg/kg every three days	CGI, PIA-CV, PPVT-III, ABC, CBCL, MCDI, SB-V. Plasma GSH and GSH/GSSG	No difference in behavioral tests or glutathione status. However, 9 (30 %) subjects showed clinically significant improvement in CGI scores and at least two additional behavioral measures. Notably, these individuals also exhibited a significant increase in plasma concentrations of GSH and in GSH/GSSG ratio.	Increased hyperactivity and increased mouthing of objects.
Vitamin/minerals supplements	Adams et al., (2011)	RCT, 2 months	141	3–60	Vit A 1000 IU Vit C 600 mg Vit D3 300 IU Vit E 150 IU Tocopherols 70 mg B1 & B2 20 mg B3 niacin 15 mg/ niacinamide 10 mg B5 15 mg B6 40 mg B12 500µg Folic Acid 100 µg Folicinic Acid 550 µg, Biotin 150 µg Choline 250 mg Inositol 100 mg Carotenoids 3.6 mg Coenzyme Q10 50 mg N-acetylcysteine 50 mg Calcium 100 mg Chromium 70µg Iodine 100 µg Lithium 500 µg Magnesium 100 mg Manganese 3 mg Molybdenum 150 µg Potassium 50 mg Selenium 22 µg Sulfur 500 mg Zinc 12 mg	Parental Global Impressions-Revised (PGI-R) Plasma sulfate, SAM, Glutathione, Nitrotyrosine, ATP, NADH, NADPH, ATP.	Significant improvements in metabolic status: total sulfate (+17 %, $p = 0.001$), SAM (+6 %, $p = 0.003$), GSH (+17 %, $p = 0.0008$), GSH/GSSG (−27 %, $p = 0.002$), nitrotyrosine (−29 %, $p = 0.004$), ATP (+25 %, $p = 0.000001$), NADH (+28 %, $p = 0.0002$), and NADPH (+30 %, $p = 0.001$). Significantly greater improvement in PGI-R ($p = 0.008$), and on the subscores for Hyperactivity ($p = 0.003$), Tantrumming ($p = 0.009$), Overall ($p = 0.02$), and Receptive Language ($p = 0.03$).	Mild behavior problems (11 %), diarrhea/constipation (11 %).
Vitamin/minerals supplements (SpectrumNeeds) and Coenzyme Q10 (QNeeds)	Hill et al., (2025) (see Table 2 for exact supplement composition)	RCT, 24 weeks, cross-over design	16	2.5–17	SpectrumNeeds is a powder with 33 active ingredients that can be mixed into liquid or food. QNeeds is gel capsule contains Ubiquinol (reduced form of coenzyme Q10). Doses vary by body weight.	Parent Rated (VABS III, ABC, CGSQ, PRASC, PRAS-ASD, SP–2), Clinician Rated (CARS, CYBOCS-ASD, CGI-I, OACIS, DAS-GCA), Citrate Synthase, Complex IV activity	Significant improvement of the VABS (daily living skills and socialization), ABC (Social withdrawal, hyperactivity), and PRASC verbal communication. Citrate synthase activity was partially normalized, and	No serious adverse events. One patient had mild transient constipation, diarrhea, and acid reflux.

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
complex IV activity (corrected for CS) showed a significant increase.								
Coenzymes/ Antioxidants								
Q10 ubiquinol	Mousavinejad et al., (2018)	RCT, 100 days	90	3–12	30 mg/day and 60 mg/day	TAS, MDA, GPx, SOD, Global impressions parental questionnaire	CoQ10 supplementation (60 mg/day) reduces GPx, SOD, and MDA, increases TAS, and improves sleep and gastrointestinal symptoms	Rarely, early CoQ10 supplementation may trigger increased hyperactivity, anger, and destructive behavior.
Q10 ubiquinol	Gvozđjaková et al., (2014)	Clinical trial, 3 months	24	3–6	50 mg twice per day	Psychological Test, plasma concentrations of TBARS, CoQ10 – TOTAL, γ - and α -tocopherol, β -carotene, and lipid peroxidation	Improved play (42 %), sleep (34 %), and food selectivity (17 %), verbal communication (21 %), communication with parents (12 %), with CoQ10 – TOTAL plasma level above 2.5 μ mol/L	Aggression (2), hyperactivity (1), sleep disorder (1).
Q10 ubiquinol	Cucinotta et al., (2022)	Observational Study, 3 months	59	2.5–39	Dose by weight ($\leq$ or >20 kg) twice a day: Q10 ubiquinol 50–100 mg, Vit E 30–60 mg, Vit B2 0.45–0.90 mg, Vit B3 5.5–11 mg, Vit B5 3–6 mg, Vit B6 0.45–0.90 mg, Vit B12 0.70–1.40 μ g, Inositol 5–10 mg	CGI	A positive outcome was recorded in 45/59 (76.27 %) patients with NDDs (CGI-I between 1 - “very much improved” and 3 - “minimally improved”). Improvements in cognition (n = 26, 44.1 %), adaptive functioning (n = 26, 44.1 %) and social motivation (n = 19, 32.2 %). More frequent improvement in Intellectual Disability compared to ASD.	Hyperactivity (9), early insomnia (6), irritability, self-aggressiveness (4), increased stereotypic behaviors (4), oppositional behavior (3), increased appetite (2).
N-acetylcysteine (NAC)	Dean, et al., (2017)	RCT, 6 months	98	3.1–9.9	500 mg /day	SRS, Children’s Communication Checklist, RBS, DBC-P, and three global impression scales, PGI-I, CGI-I/S	No significant effects were found on communication, social interaction, repetitive behaviors, problem behaviors, and parent/clinical global impression	Gastrointestinal symptoms (9), Cold (7), Ear (4), Skin (2), Fever (2), Respiratory (2), cysts (1), tonsillitis (1), aggravation of pre-existing asthma (1), dental surgery (1).
N-acetylcysteine (NAC)	Wink et al., (2016)	Pilot study, RCT, 12 weeks	31	4–12	60 mg/kg/day in three divided doses	CGI, ABC, SRS, VABS-II, Plasma GSH, GSH/GSSG ratio, DNA strand break and oxidative damage, homocysteine	No effect on CGI-I. Higher GSH in the NAC group ($p < 0.05$), with a trend also for GSSG ($p = 0.09$); no difference between NAC and placebo in GSH/GSSG ratio, DNA strand break and oxidative damage, homocysteine levels at week 12 ($p > 0.16$).	Upper respiratory infections (10), headache (3), fever (3), stomach ache (2), irritability (2), insomnia (2), otitis media (2), enuresis (1), night awakenings (1), localized rash (1), Nausea (1).
N-acetylcysteine (NAC)	Ganizadeh & Moghimi Sarani, 2013	RCT, 8 weeks	40	3.5–16	1200 mg/day in two divided doses	ABC	Significant reduction in ABC Irritability score; no effect on Lethargy and Social Withdrawal, Stereotypic Behavior, Hyperactivity and Noncompliance, and Inappropriate Speech.	Constipation (16.1 %), increased appetite (16.1 %), fatigue (12.9 %), nervousness (12.9 %), daytime drowsiness (12.9 %). stiffness (6.5 %), slow movement (6.5 %), decreased appetite (6.5 %), tremor (6.5 %), restlessness (6.5 %), Morning drowsiness (3.2 %), abdominal pain (3.2 %), itches (3.2 %),

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
Sulforaphane (SF)	Zimmerman et al., (2021)	RCT, 15 weeks	45	3–12	2.2 $\mu\text{mol/kg/day}$	OACIS, SRS–2, ABC, GSH/GSSG ratio, mitochondrial respiration, inflammatory markers and heat shock proteins.	ABC scores improved significant. No effect on OACIS (possible trend) and SRS–2. Significant changes in GSH/GSSG ratio, mitochondrial respiration, inflammatory markers and heat shock proteins.	twitches (3.2 %), blurred vision (3.2 %). Insomnia, irritability and intolerance of the taste and smell of SF.
Sulforaphane (SF)	Bent, S et al., 2018	CT, 12 weeks open label	15	7–21	222–555 μmol of glucoraphanin (GR) per day (6–15 tablets), based on body weight categories (32–105 kg)	Urinary metabolites, ABC and SRS	Clinical improvement reaching significance only for the SRS, and correlated with various metabolites involved in oxidative stress, amino acid/gut microbiome, neurotransmitters, hormones, and sphingomyelin metabolism.	Nausea, vomiting, stomach flu, g.e. reflux, weight gain, weight loss. Serious adverse events: one ruptured appendix, likely unrelated to treatment.
Sulforaphane (SF)	Singh et al., 2014	RCT, 18 weeks	44	13–27	50–150 μmol per day	ABC, SRS, CGI-I	Significant decrease in ABC scores (34 %) and in SRS scores (17 %) ($P = 0.017$). Greater number of participants in the SF group improved at the CGI-I in social interaction, abnormal behavior, and verbal communication ($P = 0.015$ – 0.007).	Vomiting, abdominal pain, increased flatulence, constipation, diarrhea, irritability, aggressivity, fever, headache, and exacerbation of seasonal allergies.
Sulforaphane (SF)	Momtazmanesh et al., (2020)	RCT, 10 weeks	60	4–12	50 μmol (≤ 45 kg) or 100 μmol (> 45 kg) per day	ABC-C	Significant decrease in Irritability ($P = 0.001$) and Hyperactivity/Noncompliance ($P = 0.015$). No significant difference in Lethargy/Social Interaction, Stereotypic Behavior, or Inappropriate Speech.	No significant difference in frequency of adverse events. Increased appetite (13.3 %) and headache (13.3 %).
Resveratrol	Hendouei et al., (2020)	RCT, Add-on, 10 weeks	62	1–12	Resveratrol (250 mg twice daily); Risperidone (twice daily starting at 0.5 mg with a dose increase of 0.5 mg per week for the first 3 weeks)	ABC-C	Greater decline in hyperactivity/non-compliance. No effect on irritability, lethargy/social withdrawal, stereotypic behavior, and inappropriate speech.	Restlessness (25.8 %), constipation (19.3 %), and diarrhea (19.3 %).
Carnosine	Mehrazad-Saber et al., (2018)	RCT, 2 months	43	4–16	500 mg/day	Children's Sleep Habits Questionnaire, Gilliam Autism Rating Scale 2	Significant improvement in daytime sleepiness, sleep duration, parasomnias, and total sleep disorder scores. No significant effect on autism severity or behavioral outcomes.	Irritation and hyperactivity, alleviated by taking the supplement with supper.
Luteolin Formulation	Theoharides et al., (2012)	Case series, 4 months	37	4–14	600 mg/20 kg body weight	Gastrointestinal (GI) and allergy symptoms, eye contact & attention, social interactions, & speech (measurement test for these domains were not specified)	GI and allergy symptoms improved in approximately 75 % of children, eye contact and attention in 50 %, social interaction in 25 %, and the resumption of speech in about 10 %.	There were no adverse effects.
Probiotics Probiotic	Russo, (2014)	Cross Sectional Study	49	Mean age 10.2–11.4	Not reported	Plasma myeloperoxidase (MPO), plasma copper and zinc	MPO levels ($P = 0.0009$), and plasma copper ($P = 0.02$) in individuals	Not reported.

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
Probiotic <i>Lactobacillus plantarum</i>	Sherman et al., (2022)	RCT, 16 weeks	35	3–20	6 × 1010 CFUs	SRS, ABC–2, CGI, SpCO level, fecal microbiome, serum inflammatory markers, autoantibodies, and oxytocin.	taking probiotik therapy significantly lower compared to those not taking probiotics. No difference in plasma zinc levels in the probiotic group. Improved SRS motivation and ABC–2 inappropriate speech. In the treatment group, ASD severity was significantly correlated with baseline SpCO ($p = 0.029$), anti-lysoganglioside GM1 ($p = 0.022$), anti-tubulin ($p = 0.042$), and anti-D1 ($p = 0.045$).	Not reported.
Natural treatments and Other Supplements								
Ginkgo biloba	Hasanzadeh et al. (2012)	RCT, Add-on, 10 weeks	47	4–12	Ginkgo biloba 80 mg/day for patients under 30 kg and 120 mg/day above 30 kg	ABC-C, The Side Effect Checklist	No effect on the 5 subscales of the ABC-C rating scale.	No significant difference in frequency of adverse events. Drowsiness (8), Constipation (3), Dizziness (1), Slowed movement (2), Nervousness (5), Restlessness (3), Increased appetite (6), Loss of appetite (3), Fatigue (5), Diarrhea (3), Twitches (3), Drymouth (1), Trouble swallowing (1), Sore throat/tongue (1), Abdominal pain (2). Not reported.
Cacao	Sadek et al., (2018)	Clinical Trial, 4 weeks	17	4–17	16 g per day of dark chocolate containing 70 % cacao and 30 % organic cane sugar.	ABC–2, ASRS	Significant improvement in ABC–2 irritability ($P = .03$), social withdrawal ($P = .01$), stereotypic behavior ($P = .05$), hyperactivity/noncompliance ($P = .04$), and inappropriate speech ($P = .05$). Significant improvement in ASRS unusual behaviors ($P = .003$), self-regulation ($P = .02$), social/communication ($P = .04$), and total scores ($P < 0.001$).	Not reported.
Camel milk	Al-Ayadhi and Elamin, (2013)	RCT, 2 weeks group I: raw milk group II: boiled milk group III: placebo	60	2–12	500 mL/day	CARS Glutathione (GSH), superoxide dismutase (SOD), myeloperoxidase (MPO)	CARS Score significant increase in groups I and II ($P = 0.004$, $P = 0.001$, resp.), not in group III. GSH levels were significantly increased in groups I and II ($P = 0.05$, $P = 0.02$, resp.), not in group III. Significant increase in SOD plasma levels only in group II ($P = 0.007$). Significant Increase MPO in groups I ($P = 0.05$), and II ($P = 0.02$), not in group III.	Not reported.
Cysteine-rich whey protein isolate (CRWP)	Castejon et al., (2021)	RCT, 90 days	46	3–5	0.5 g/kg if < 20 kg 10-g/day if > 20 kg	SCQ, MSEL, VABS-II, CBC, Glutathione levels.	Significant improvement in VABS-II behavioral assessment	Bronchitis/cough/respiratory infection (4). Cold symptoms

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
							(effect size 0.98, $P = 0.03$) and in VABS-II adaptive behavior ($P = 0.03$), socialization ($P = 0.03$), maladaptive behavior ($P = 0.04$), and internalizing behavior ($P = 0.02$) domains. Significantly increased glutathione levels ($P = 0.04$).	(9), Constipation (1), Diarrhea (4), Emesis/nausea (7), Fever (4), Rash (1), Other/etc (4).
Pharmacotherapy								
Sapropterin	Frye et al., (2013)	Clinical trial, 16 weeks	10	2–6	20 mg/kg per day	PLS, VABS, ABC, and ASQ, Pterin, redox balance, nitric oxide (NO)	Significant improvement in several subscales of the PLS, VABS, ABC, and ASQ influenced by baseline levels and changes in several biomarkers related to pterin, redox balance, and NO.	Irritability, excitement, mild upset stomach (10 %), and insomnia (10 %).
Intervention Therapies								
Hyperbaric oxygen therapy (HBOT)	Rossignol et al., (2007)	Pilot study, Clinical Trial, 40 sessions	18	3–16	40 hyperbaric sessions of 45 min duration each at either 1.5 atmospheres (atm) and 100 % oxygen, or at 1.3 atm and 24 % oxygen	ABC-C, SRS, ATEC, C-reactive protein (CRP), Plasma Oxidized Glutathione (GSSG).	HBOT at 1.3–1.5 atm with 24–100 % oxygen did not produce a significant reduction in mean ABC-C scores. Significant reductions in SRS and ATEC scores. Decreased CRP levels, without increasing oxidative stress. CRP reductions were greater in children with elevated baseline levels.	No significant adverse events.
Hyperbaric oxygen therapy (HBOT)	Chungpaibulpatana et al., (2008)	Clinical Trial, 10 sessions	7	5–9	HBOT 1.3 atm., 100 % oxygen concentration, once a week	Social development, Fine motor and Eye-hand coordination, Language development, Gross motor development, Self - help skills	Seventy-five percent of children showed significant improvement across all five domains, with 33.3 % exhibiting notable gains in sleep, cognitive abilities, social skills, flexibility, and problem-solving.	No serious adverse effects were reported, except for mild tinnitus in one case, which resolved within a week.
Hyperbaric oxygen therapy (HBOT)	El-baz, F., 2014	Clinical Trial, 20–40 sessions	20	2–9	HBOT 1.5 ATA, 100 % oxygen for 1–1.5 hrs per session, in either multi- or mono-place chambers; 20–40 sessions.	CARS, ATEC	Significant improvement in ATEC total score, ATEC subscales (communication, sociability, cognitive awareness, and behavior), and CARS.	Not reported
Hyperbaric oxygen therapy (HBOT)	Peterson et al., (2024)	Clinical Trial, 40 sessions	65	2–17	Minimum of 40 HBOT treatments, breathing 100 % oxygen at 2.0 atmosphere absolute (ATA) for 60 min.	VBMAPP, ABLLS	Significant improvement ($p < 0.05$) in all VBMAPP milestone domains and total score.	Ear discomfort (12.5 %), vomiting (3.1 %), dyspnea (3.1 %), and sinus congestion (3.1 %).
Cleanroom technology	Faber et al., (2015)	Clinical Trial, 2 weeks	10	3–12	10 h each evening in the cleanroom while wearing silk or cotton clothes.	Blood and hair magnesium, iron, selenium, zinc, aluminum, antimony, arsenic, cadmium, chromium, lead, manganese, mercury, nickel, and tin. Organic toxins (benzene, toluene, and o-xylene). Marker of Oxidative stress (GSH, GSSG, GSH/GSSG). Markers of immune	At the age of 6, a significant difference tended to occur in the direction of change for some elemental nutrients (iron, magnesium, selenium, and zinc), organic toxicants (benzene and PCB 28), and immune markers (CD3 % and CD4 %). The behavior of younger children improved more than older children at	Not reported.

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Table 1 (continued)

Medication	Reference	Study design, duration	Sample size	Age (yr)	Mean dose	Outcome measures	Therapeutic effects	Side effects reported in the treated group (n)
						dysregulation (CD3 %, CD4 %, WBC, IgA, plasma zinc/serum copper ratio). Behavioral rating scales (SCQ, ABC, CARS, PDDBI, REXSCA/C, GARS-2, ATEC)	the SCQ, PDDBI, and ABC.	

*abbreviation, ABC: Aberrant Behavior Checklist; ABC-2: Aberrant Behavior Checklist, 2nd ed; ABC-C: Aberrant Behavior Checklist -Community; ABLLS: The Assessment of Basic Language and Learning Skills; ADMA: Asymmetric-dimethylarginine; ASQ: Autism Symptoms Questionnaire; ASRS: Autism Spectrum Rating Scale; Anti-D1: ATP: Adenosine Triphosphate; Anti-dopamine Receptor D1; Anti-GM1: Anti-lysoganglioside GM1; CaMK II: Calcium Calmodulin-dependent Protein Kinase II; Autism Symptoms Questionnaire; ASRS: Autism Spectrum Rating Scale; ATEC: Autism Treatment Evaluation Checklist; CARS: The Childhood Autism Rating Scale; CBCL: Child Behavior Checklist; CD3 %: Total T cell percent; CD4 %: Helper T cell percent; CD4/CD8: Helper/Suppressor ratio; CFU: Colony Forming Unit; CGI: Clinical Global Impression Scale; CGI-I: Clinical Global Impression Improvement Scale; CGI-S: Clinical Global Impression Severity Scale; CGSQ: Caregiver Strain Questionnaire-Short Form; CYBOCS-ASD: Children's Yale-Brown Obsessive-Compulsive Scales-ASD; DAS-GCA: Differential Abilities Scale-General Cognitive Ability; DBC-P: The Developmental Behaviour Checklist-Primary Carer Version; ESRS: The Extrapyrimal Symptom Rating Scale; GARS-2: Gilliam Autism Rating Scale-2; GPx: Glutathione Peroxidase Activity; GSH: Reduced glutathione; GSH/GSSG: Reduced glutathione/oxidized glutathione ratio; GSSG: Oxidized glutathione; MCDI: MacArthur Communication Developmental Inventory; MDA: malondialdehyde; MSEL: Mullen scales of early learning; NADH: Nicotinamide Adenine Dinucleotide; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; OACIS: Ohio Autism Clinical Impressions Scale; PDDBI: PDD Behavioral Inventory; RBC: Red blood cell; RCF: Relative centrifugal force; REXSCA/C: Receptive/Expressive Social Communication Abilities Composite; SCQ: Social Communication Questionnaire; SENSORY: Sensory/Perceptual Approach Behaviors; PEP-3: Psychoeducational Profile-third edition; PGI-I: The Parent Global Impression-Improvement scale; PGI-R: Parental Global Impressions-Revised; PIA-CV: Parent Interview for Autism-Clinical Version; PRASC: Parent Rated Autism Symptomatic Change Scale; PLS: Preschool Language Scale; PPVT-III: Peabody Picture Vocabulary Test Third Edition; PRAS-ASD: Parent-Rated Anxiety Scale for Youth with Autism Spectrum Disorder; RBS-R: The Repetitive Behavior Scale-Revised; SAM: Methionine, S-adenosylmethionine; SAH: S-adenosylhomocysteine; SB: Stanford Binet V Edition; SpCO: Carboxyhemoglobin; SCQ: Social communication questionnaire; SOD: Activity Superoxide Dismutase; SP2: Sensory Profile 2; SRS: Social Responsiveness Scale; SRS-2: Social Responsiveness Scale-2; TAS: Total antioxidant status; TBARS: Thiobarbituric acid reactive substances; tGSH: Total glutathione; tGSH/GSSG: Total glutathione/oxidized glutathione ratio; VABS: Vineland Adaptive Behavior Scale; VABS-II: Vineland Adaptive Behavior Scale, 2nd edition; VABS III: Vineland Adaptive Behavior Scale; VBMAPP: Verbal Behavior Milestones Assessment and Placement Program; WBC: White blood cell.

3.2. Coenzymes/ Antioxidants

Several coenzymes and antioxidants have been investigated for their potential benefits in ASD, with varying efficacy. Ubiquinol, the reduced form of Coenzyme Q10, has shown promise in improving cognition, adaptive functioning, and social motivation, especially in children with intellectual disabilities, by supporting mitochondrial function (Cucinotta et al., 2022; Gvozdjaková et al., 2014 but also see Longevity OMAC, 2020; Persico et al., 2023). A 60 mg/day dose reduced oxidative stress markers, increased antioxidant capacity, and improved sleep and gastrointestinal symptoms (Mousavinejad et al., 2018). Sulforaphane, derived from cruciferous vegetables, enhances glutathione synthesis, reduces oxidative stress, and improves irritability and hyperactivity (Zimmerman et al., 2021; Momtazmanesh et al., 2020; Singh et al., 2014), with these effects linked to increased neurotransmitters, amino acids, sphingomyelin, and stress-related hormones (Bent and Hendren, 2010). N-acetylcysteine (NAC) replenishes glutathione and reduces irritability, particularly when used with risperidone (Ghanizadeh, Moghimi-Sarani, 2013; Wink et al., 2016), but did not show significant improvements in core ASD symptoms (Dean et al., 2017). Resveratrol, despite its antioxidant properties, has not shown significant effects on irritability or core symptoms but may reduce hyperactivity (Hendoue et al., 2020). Carnosine improved sleep, but did not significantly affect behavioral or ASD severity (Mehrazad-Saber et al., 2018). Luteolin, an anti-inflammatory flavonoid, alleviates gastrointestinal and allergy symptoms in ASD and shows some improvement in attention and social interaction, though evidence is limited only to open clinical trials (Theoharides et al., 2012; Persico et al., 2025).

3.3. Probiotics

Probiotics have gained attention as a potential therapeutic option for ASD, particularly due to evidence of gut dysbiosis in both humans and

animal models (Sgritta et al., 2019). Their impact on gut health and inflammation has spurred multiple studies, reviewed elsewhere (Persico et al., 2025), but research on their mediation of benefits through reduced oxidative stress in ASD is more limited. Sherman et al. (2022) found that *Lactobacillus plantarum* improved core ASD symptoms, including social motivation and inappropriate speech, while reducing autoimmunity markers and gut-related symptoms. Russo (2014) showed that probiotic therapy significantly lowered plasma myeloperoxidase (MPO) and copper levels, suggesting a possible impact on inflammatory pathways. These findings suggest that probiotics may influence redox status by modulating inflammatory pathways and gut microbiome composition, in ways that also yield small-to-moderate improvement in social communication and behavior, but more research is needed to confirm their effectiveness and optimal strain composition.

3.4. Natural treatments and other supplements

Despite its well-established antioxidant and anti-inflammatory properties, Ginkgo biloba did not significantly improve treatment outcomes, as measured by the Aberrant Behavior Checklist-Community (ABC-C), nor the side effect profile, when administered as an adjunct therapy to risperidone in an RCT involving 47 children with ASD (Hasanzadeh et al., 2012). In contrast, camel milk and cysteine-rich whey protein isolate (CRWP) have shown promising effects in improving oxidative stress and behavioral symptoms in children with ASD. Both raw and boiled camel milk significantly reduced oxidative stress in 60 children with food allergies and intolerance, while improving autistic behaviors, though the effects were modest (Al-Ayadhi and Elamin, 2013). Notably, boiled camel milk had a stronger effect on increasing glutathione (GSH), superoxide dismutase (SOD), and myeloperoxidase (MPO) levels, and decreasing CARS scores, suggesting processing-related differences. Additionally, an RCT with CRWP in 46 children showed significant improvements in glutathione

Strategies to break the cycle of oxidative stress and improve behavioral health in ASD

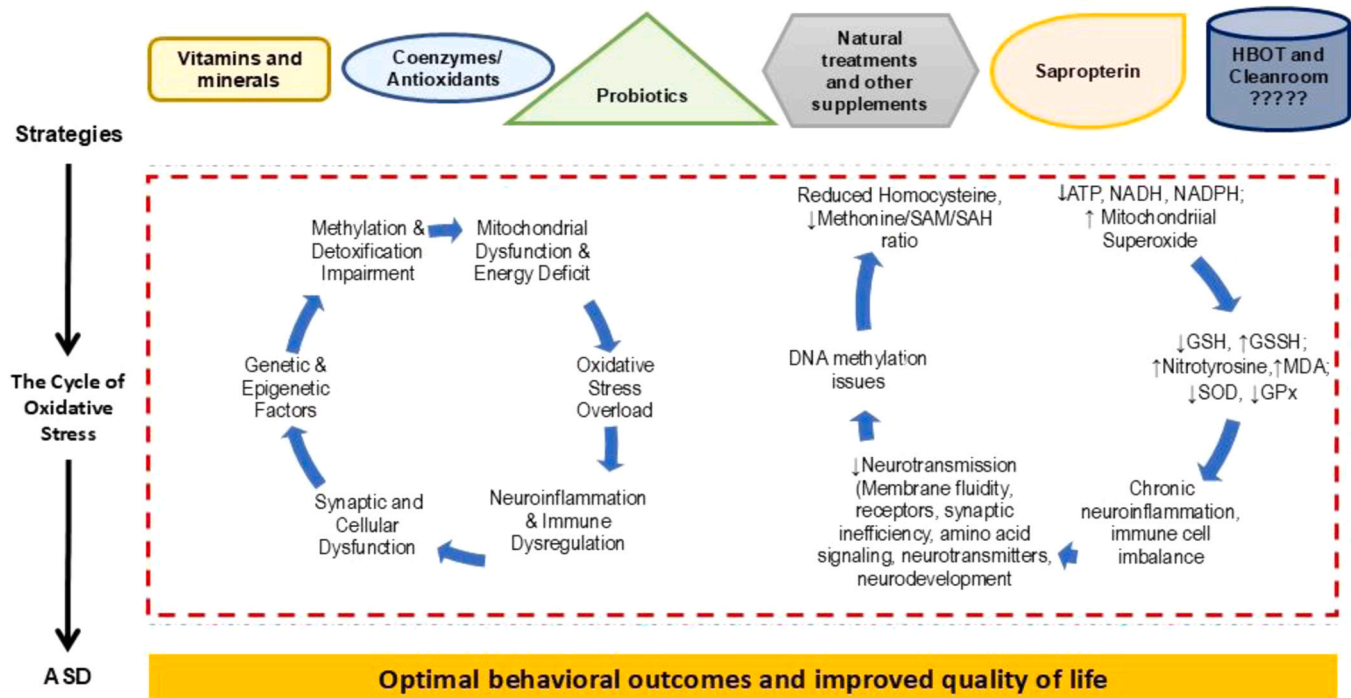


Fig. 2. The Strategies to Break the Cycle of Oxidative Stress to Improve Behavioral Health in ASD.

levels and behavioral measures, including adaptive behavior, socialization, and reductions in maladaptive and internalizing behaviors (Castejon et al., 2021). Similarly, broad-spectrum behavioral benefits were reported with 16 g per day of dark chocolate containing 70 % cacao, but the evidence is limited to only one open clinical trial (Sadek et al., 2018). These findings suggest that camel milk and CRWP, but not Ginkgo biloba, may provide small-to-moderate benefits in improving both metabolic and behavioral symptoms in ASD, while evidence on cocoa is still too limited. In all cases, further research is needed to confirm efficacy and address underlying mechanisms.

3.5. Pharmacotherapy

Sapropterin is a synthetic form of tetrahydrobiopterin (BH4), commonly used in the treatment of phenylketonuria (PKU) to lower phenylalanine levels. Beyond this primary use, sapropterin also acts as an antioxidant by modulating nitric oxide (NO) metabolism, which has been shown to be overproduced in individuals with autism spectrum disorder (ASD) (Sogut et al., 2003). A preliminary study involving 10 patients demonstrated that sapropterin treatment significantly improved several oxidative stress biomarkers, including the ratio of reduced-to-oxidized pterin in serum, overall redox status, and NO metabolism (Frye et al., 2013). In addition to biochemical improvements, behavioral gains were also observed across various domains of adaptive functioning and problem behaviors. Notably, the extent of behavioral improvement was influenced by each patient's pre-treatment NO activation status (see Table 1). However, due to the small sample size, these promising findings should be interpreted with caution and confirmed through larger, controlled studies.

3.6. Interventions with no evidence of efficacy

Several studies have explored the effects of Hyperbaric Oxygen Therapy (HBOT) and cleanroom environments on children with Autism Spectrum Disorder (ASD). Rossignol et al. (2007) reported significant

reductions in SRS (Social Responsiveness Scale) and ATEC (Autism Treatment Evaluation Checklist) scores, as well as decreased C-reactive protein levels without increased oxidative stress, in 18 children after 40 HBOT sessions at 1.3–1.5 atm. Chungpaibulpatana et al. (2008) observed improvements in social, motor, language, and self-help skills in 7 children receiving weekly HBOT at 1.3 atm. El-baz et al. (2014) found reductions in ATEC and CARS scores in 20 children who underwent 20–40 sessions at 1.5 atm. In a larger trial, Peterson et al. (2024) demonstrated significant gains across all VB-MAPP (Verbal Behavior Milestones Assessment) and ABLLS (The Assessment of Basic Language and Learning Skills) domains in 65 children after ≥ 40 sessions at 2.0 atm. Importantly, all four these studies are open clinical trials and, to our knowledge, no RCT on HBOT has ever been performed in ASD.

Faber et al. (2015) employed “cleanroom sleeping environments” (CSE) in an open study involving 10 children with ASD, 3–12 years old, who slept in a cleanroom for two weeks to minimize exposure to airborne toxins and pollutants. The authors claim that CSE significantly reduced oxidized glutathione levels, improved immune dysregulation markers, and improved behavioral parameters, particularly in younger children. Their data actually indicate that no more than two children may have undergone any improvement (Faber et al., 2015). Drawing any conclusion from an open trial involving such a small patient sample is indeed hazardous. These reports exemplify the need for scrutiny of study quality by readers, even for studies that may have undergone a peer-review process.

3.7. Limitations

Despite the promising data outlined above, the Literature concerning interventions against oxidative stress and their possible efficacy in ASD display several limitations which must indeed be considered. The number of studies is limited. Many studies have small sample sizes and exhibit significant heterogeneity in participant characteristics, potentially affecting the generalizability of the findings. Additionally, the short duration of interventions in many studies does not provide

information on long-term efficacy and safety, raising uncertainty on the long-term effects of antioxidant treatments. The methodologies employed are diverse, with a notable paucity of high-quality randomized controlled trials (RCTs). A critical appraisal of published studies by readers is recommended, especially in reference to the quality of study design, patient selection bias, and potential conflicts of interest.

4. Conclusions

This scoping review summarizes current strategies aimed at breaking the cycle of oxidative stress in order to improve behavioral health in individuals with Autism Spectrum Disorder (Fig. 2). Genetic and epigenetic vulnerabilities often concerning common variants, impaired methylation, mitochondrial dysfunction, oxidative stress, neuro-inflammation, and synaptic impairment culminate in worsening the core symptoms of ASD and reducing quality of life above and beyond the limitations that the diverse genetic and epigenetic aetiologies of ASD would have yielded *per se*. The various therapeutic strategies summarized in this review have shown potential in disrupting this cycle by restoring redox balance and enhancing mitochondrial function, thereby contributing to improve behavioral outcomes in individuals with ASD, by relieving this additional layer of metabolic dysfunction.

Collectively, current findings suggest that improving metabolic function and reducing oxidative stress may play a role as an adjunct therapy in ASD, albeit yielding small-to-moderate improvement most likely in specific subgroups of children (Nordahl et al., 2022). While awaiting for the development of genetically-designed personalized therapies, even small improvements obtained with excellent risk-benefit ratios are indeed of great interest.

Elevated oxidative stress and the decrease in antioxidant capacity represent in many individuals with ASD influence various aspects of neurodevelopment, eventually affecting also their behavior and social functioning, in addition to their broader health status. Therapeutic strategies aimed at reducing oxidative stress have shown promising results in progressing the quality of life for individuals with ASD. By integrating this knowledge into a multidisciplinary framework, the management of ASD can be enhanced not only in terms of alleviating behavioral symptoms but also in improving the overall well-being of affected individuals. This review has highlighted the benefits of using vitamins in daily practice, particularly in terms of the reduced risk of severe adverse reactions. Additionally, vitamins are widely available and low-cost, making them especially relevant for Asian countries, including Indonesia. However, further large-scale clinical trials applying the rigorous methodologies routinely used in pharmaceutical research to nutraceuticals, paired with the development of biomarkers to identify sensitive patients, are now needed to conclusively identify effective therapies and integrate them into the clinical management for optimal behavioural outcome of ASD.

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Antonio M. Persico: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization, Funding acquisition. **Rinvil Renaldi:** Writing – original draft, Investigation, Funding acquisition,

Formal analysis, Data curation. **Tjhin Wiguna:** Writing – review & editing, Supervision, Conceptualization. **Andi Jayalangkara Tanra:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no competing interests

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2025.104575.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study

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