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The Role of Microbiota Metabolites Propionic Acid, p-Cresol, and 4-Ethylphenyl Sulfate in Autism Susceptibility: A Systematic Review

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ABSTRACT

The etiopathogenesis of Autism Spectrum Disorder (ASD) encompasses complex interactions between genetic and environmental risk factors. The high prevalence of gastrointestinal disorders in autistic individuals has propelled a growing interest in the possible involvement of gut dysbiosis in ASD pathogenesis. Thousands of different bacterial strains are found in the human gut, which produce numerous metabolites that can enter the bloodstream and often pass the blood–brain barrier, potentially influencing neurodevelopment and brain function. This systematic review aims to provide a comprehensive outlook on the role of three metabolic compounds derived from gut bacteria, propionic acid (PPA), p-cresol, and 4-ethylphenyl sulfate (4-EPS), in modulating neuronal function and conferring susceptibility to ASD. To achieve this, we screened 411 records collected through a systematic search of current scientific literature in PubMed, Web of Science, and Scopus, ultimately reviewing a total of 90 records, which included data from ASD human cohorts as well as animal and cellular models of autism. Human studies provided compelling evidence of altered metabolic profiles in ASD individuals, especially for PPA and p-cresol, but also to a smaller extent, for 4-EPS. Furthermore, data obtained from the exposure of experimental models to each one of these three metabolic compounds identified several behavioral anomalies induced in treated animals and highlighted common neurobiological mechanisms. Overall, current literature supports the contribution of gut metabolites to ASD susceptibility and/or a significant modulatory role on the clinical expression of ASD, strongly encouraging further research in the field in order to improve autism diagnostics and management.

1 | Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by social impairment and communication deficits, restricted interests, stereotyped behaviors, and sensory processing anomalies (Lord et al. 2020). It usually emerges in early childhood with little evidence for remission later in life and affects approximately 1%–2% of the general population, making it one of the most common conditions in child neuropsychiatry (Baxter et al. 2015; Maenner et al. 2023; Scattoni et al. 2023). The clinical presentation of ASD is highly heterogeneous in terms of behavioral symptoms, associated

Summary

Data supporting a potential involvement of gut bacteria and their metabolites in autism has recently emerged. Specifically, three metabolic compounds (propionic acid, p-cresol, and 4-ethylphenyl sulfate) produced by gut bacteria are among the best candidates as contributors to autism. This review is, to our knowledge, the first to gather results regarding these three compounds and their role in autism susceptibility, identifying differences and commonalities in their mechanisms of action on neuronal cells and on the developing brain. It also discusses their potential use as biomarkers or as drug targets for future treatments.

conditions and severity. Etiology is also highly complex, with numerous established genetic and environmental risk factors (Lord et al. 2020). Twin and family studies of ASD have demonstrated its high heritability, with phenotypic concordance in monozygotic twin pairs ranging from 60%–90% (Bourgeron 2015). However, single genetic variants are the sole or main cause of ASD in a minority of cases, though sizable, while the majority may require complex gene–gene and gene–environment interactions involving numerous risk factors, the best established being elevated parental age, perinatal damage, and gestational diabetes (Lord et al. 2020).

Cohort studies have conclusively shown a higher incidence of gastrointestinal (GI) disorders in autistic children compared to neurotypical peers (Leader et al. 2022). These data, along with the growing recognition of an existing gut-brain axis that influences mental health and brain development (Cryan 2025), led to a steadily growing field of research focused on the relationship between gut dysbiosis and autism. Despite large between-study heterogeneity, ASD children tend to display reduced variety in gut bacterial strains, decreased beneficial strains like *Bifidobacterium* and *Lactobacillus*, and increased potentially harmful bacteria related to *Enterocloster clostridioformis* (former *Clostridium clostridiforme*) and *Desulfovibrio*, compared to neurotypical peers (Finegold et al. 2010). These findings have recently encouraged the design of small open-label clinical trials testing the effects of microbiota transfer therapy (MTT) that, despite limitations, showed promising results in the treatment of GI disorders and improvement in cognitive and behavioral symptoms (Kang et al. 2017, 2020).

The gut microbiota produces countless metabolites, including small neuroactive molecules able to pass the blood–brain barrier and to influence neuronal function and/or brain development. Short-chain fatty acids (SCFAs), neurotoxins, neuromodulators and neurotransmitter precursors represent examples of compounds either produced by the gut microbiota or derived from host-bacteria co-metabolism. SCFAs, such as acetic, propionic, and butyric acids, are mostly derived from the microbiota-mediated anaerobic fermentation of indigestible polysaccharides; these molecules can cross the blood–brain barrier and influence brain function either directly or indirectly (Canada et al. 2025; Silva et al. 2020). Specifically, propionic acid (PPA) and its conjugate base, propionate, exert numerous neurobiological effects, including disturbance of neurotransmission, neural cell proliferation and differentiation, neuroinflammation, and mitochondrial damage. These neurobiological insights, together with the behavioral findings from PPA intoxication in animal models, established the compound as a chemical inducer of ASD (Csoka et al. 2024).

Among the most investigated neuroactive compounds produced by the gut microbiota and possibly involved in ASD are also p-cresol and its primary human metabolite, p-cresylsulfate (p-CS), a known uremic toxin (Flynn et al. 2025; Persico and Napolioni 2013; Renaldi, Wiguna, et al. 2025). P-cresol, also known as 4-methylphenol, belongs to the cresol class of organic aromatic compounds. Environmental exposure derives either from ingestion, inhalation, or skin contact with p-cresol released in nature through the photo-oxidation of toluene, or, more importantly, from over 55 species of gut bacteria that produce p-cresol as a byproduct of tyrosine and phenylalanine fermentation, primarily *Blautia hydrogenotrophica*, *Clostridioides difficile*, *Olsenella ulli*, and *Romboutsia liuseburensis* (Flynn et al. 2025; Persico and Napolioni 2013). P-cresol and p-CS have been proposed to exert a range of effects, either directly on neurodevelopment and on various neurotransmissions, or indirectly by modulating brain neuroinflammation and metabolism (Bermudez-Martin et al. 2021; Liu et al. 2022; Pascucci et al. 2020).

In recent years, another uremic toxin, 4-ethylphenyl sulfate (4-EPS), has emerged as a potential new contributor to autism pathophysiology. 4-EPS is structurally related to pCS but is derived from 4-ethylphenol. Similarly to p-cresol and pCS, 4-EPS is derived from bacterial fermentation of the amino acid tyrosine and, to a minor extent, phenylalanine (Figure 1). Research on 4-EPS is still limited, but available data suggest significant effects on brain and behavior (Needham et al. 2022).

Given the increasing interest in the field of autism research for these three metabolites, we planned this systematic review to summarize both distinctive and shared mechanisms of action, behavioral effects and clinical correlates, providing a broad overview of current evidence provided by cellular, animal and human studies. This systematic approach allowed us to highlight and validate consistent findings about the three compounds and to identify gaps in the existing literature.

2 | Materials and Methods

2.1 | Study Design and Data Sources

The systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on December 2, 2024, with id. CRD42024617078. Studies were identified through a systematic search of the following databases: PubMed, Scopus, and WebOfScience (WOS) (date of first search: 16 December 2024; date of last update: 28 April 2025). The three different compounds (propionic acid, p-cresol and 4-EPS) were searched separately with the three different search strings reported in Table 1 and implemented in each database. All searches were limited to title and abstract.

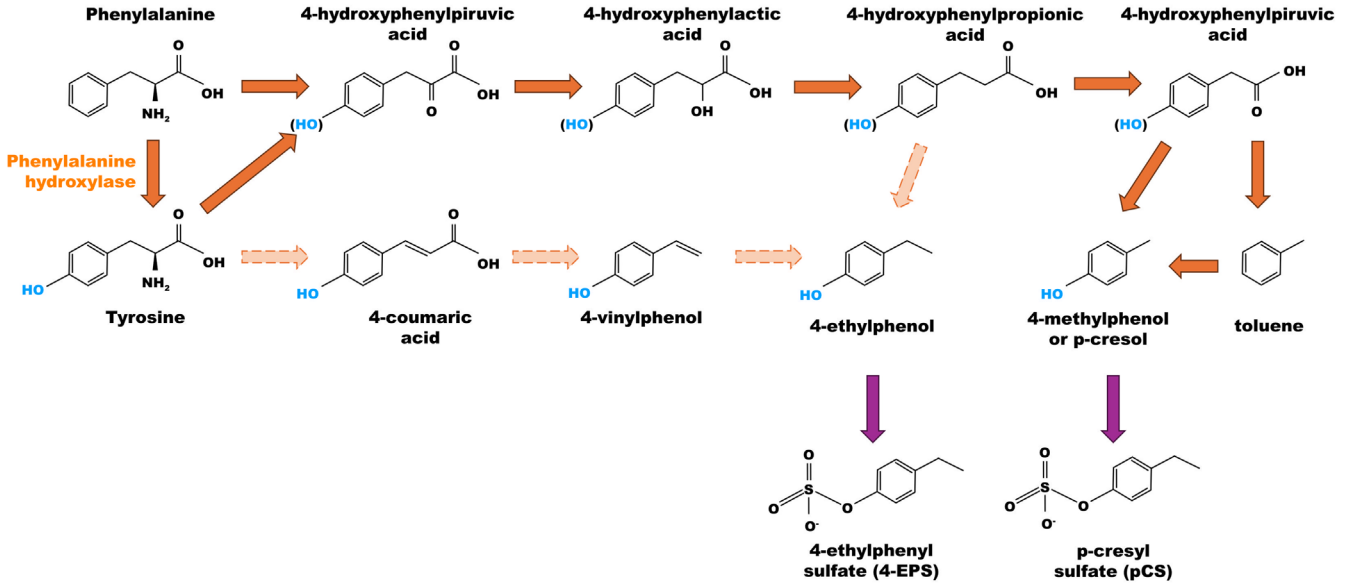

FIGURE 1 | Tyrosine and phenylalanine metabolism in the human gut. Gut microbiota metabolism (orange arrows) drives tyrosine and phenylalanine metabolic transformation into 4-ethylphenol and p-cresol. The sulfate conjugates 4-ethylphenyl sulfate (4-EPS) and p-cresyl sulfate (p-CS) are then generated by the host metabolism (purple arrows). Solid arrows indicate established reactions, while hyphenated arrows signal alleged reactions (from Zheng et al. 2021, modified).

TABLE 1 | Search strings for identification of relevant studies from Pubmed, Scopus and WebOfScience (limited to title-abstract).

Metabolite	Search string
Propionic acid	(autism OR autistic OR pervasive OR Asperger) AND ("propionic acid" OR "propanoic acid" OR propionate)
P-cresol	(autism OR autistic OR pervasive OR Asperger) AND (p-cresol OR "p-cresyl sulfate" OR cresol OR 4-methylphenol)
4-EPS	(autism OR autistic OR pervasive OR Asperger) AND (4-ethylphenyl OR 4-EPS OR 4EPS)

2.2 | Study Inclusion and Exclusion Criteria

A detailed flowchart outlining the systematic search and selection process employed in this study is presented in Figure 2. Only research articles published in peer-reviewed journals were included in the analysis; therefore, reviews, meta-analyses, case reports, opinion articles, books, and book chapters were excluded. Studies were also excluded if they were not related to the topic of this review, specifically: (a) the effects of three microbiota-derived metabolites (PPA, p-cresol, and 4-EPS) on physiological function and/or brain development, and (b) their possible contribution to the clinical phenotype of ASD.

To obtain the most comprehensive outlook on the topic, we included both human cohort studies and experimental models in vitro or in vivo. Some PPA in vivo research models, however, were excluded as "wrong outcome" (Figure 2), because they did not assess the effect of the metabolite on neural function and/or brain development, but were used exclusively as an established animal model of ASD to test potential therapeutic compounds not specifically related to PPA itself. These investigations fall outside the scope of this systematic review.

2.3 | Study Selection Process

The initial search, conducted by LS, yielded 872 records, including 239 from PubMed, 238 from WOS, and 395 from Scopus. After the removal of duplicates ($n=461$), two authors (LS and LA) screened the remaining 411 records (Suppl. Table S1) for eligibility based on title and abstract to eliminate articles written in languages not spoken by any of the authors, that is, English, Italian, French, or Spanish ($n=8$), types of publications not included ($n=142$), and research articles investigating unrelated topics ($n=72$). The remaining records were analyzed through full-text analysis by three authors (LS, LA, and NG), and were excluded if not assessing the effect of each metabolite on brain physiology and/or development ($n=93$), investigating non-autistic patient populations ($n=6$), not focused on experimental animal models of ASD employing PPA, p-cresol/p-CS, or 4-EPS ($n=5$), and if describing computational models without presenting empirical findings ($n=1$). This process left 84 records, which were completed by the addition of a small number of studies ($n=6$) identified through the reference lists of published review articles (Figure 2).

At the end of the process, a total of 90 research articles were included in the final analysis. The vast majority ($n=61$) investigated the link between propionic acid exposure and autism; a considerable number ($n=31$) were related to the role of p-cresol in ASD; the role of 4-EPS in autism was addressed only by 6 articles. Several studies investigated two metabolic compounds.

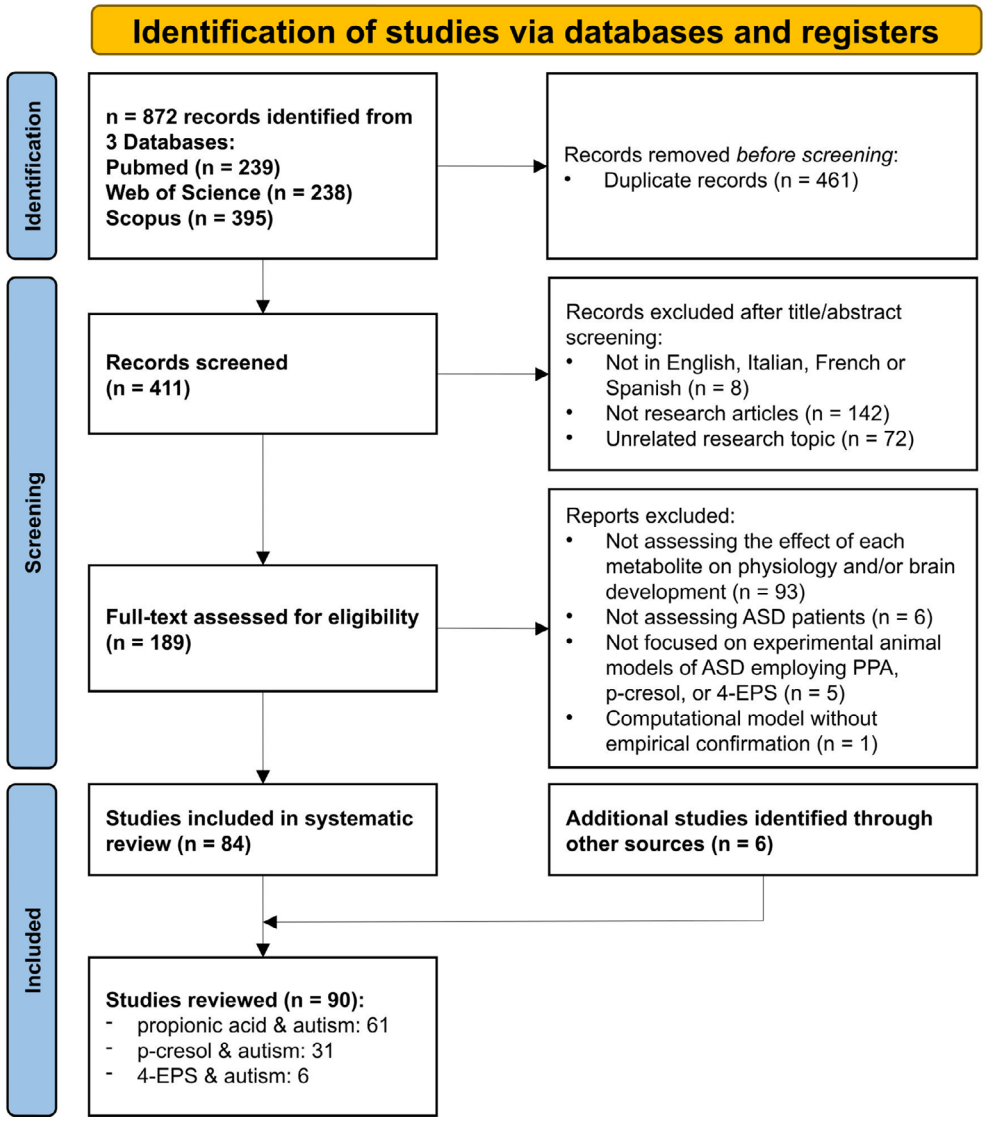

FIGURE 2 | Prisma chart diagram. Flow chart representing the methodology for the screening and identification of records.

3 | Results

3.1 | Studies in Human ASD Cohorts

Overall, a total of 35 studies investigated the correlation between ASD and altered levels of PPA, p-cresol, and 4-EPS, either quantifying metabolites in biological samples from autistic individuals or in a small percentage of reports, by evaluating the incidence of ASD in propionic acidemia, a rare autosomal recessive condition (OMIM #606054) caused by the deleterious genetic inactivation of propionyl-CoA carboxylase leading to accumulation of PPA and its toxic derivatives in blood (Shchelochkov et al. 2024). Table 2 summarizes the most relevant findings from the 35 human studies and highlights differences and common patterns between the three compounds. Suppl. Table S2 details relevant data extracted from each human study. PPA and p-cresol were widely studied, with 19 and 20 research articles, respectively. 4-EPS was by far the least investigated, with only 3 published studies assessing this compound in ASD individuals.

3.1.1 | Propionic Acid Levels in Autistic Children and Neurodevelopmental Insights From Propionic Acidemia

Levels of propionic acid were primarily investigated in fecal samples from autistic versus neurotypical children, with only one study assessing plasma levels of PPA. Conflicting findings were reported, with a slight majority of studies indicating an overabundance of PPA in fecal samples from ASD cohorts (Coretti et al. 2018; De Angelis et al. 2013; Deng et al. 2022; He et al. 2023; Vernocchi et al. 2023; Wang et al. 2012), but still a considerable number of studies reporting fecal levels of PPA either similar (Ha et al. 2021; Laue, Bauer, et al. 2024; Laue, Bonham, et al. 2024; Wang et al. 2019) or even lower (Adams et al. 2011; Wang et al. 2020) in affected individuals compared to neurotypical controls. In addition, one record analyzing microbiota composition and SCFAs concentration over 6 months found these parameters greatly influenced by dietary habits and changing over time in ASD children (Berding and Donovan 2020). Lower plasma PPA concentrations were found in an ASD cohort compared to neurotypical controls

TABLE 2 | Summary of main findings from 35 human cohort studies.

		Propionic acid (19 studies)	P-cresol (20 studies)	4-EPS (3 studies)
Metabolite levels in ASD bio-samples	Increased in ASD patients	Coretti et al. 2018 (F) De Angelis et al. 2013 (F) Deng et al. 2022 (F) He et al. 2023 (F) Vernocchi et al. 2023 (F) L. Wang et al. 2012 (F)	Altieri et al. 2011 (U) Chen et al. 2019 (U) De Angelis et al. 2013 (F) Gabriele et al. 2014 (U) Gabriele et al. 2016 (U) Gevi et al. 2020 (U) Kang et al. 2018 (F) Li et al. 2018 (U) Mussap et al. 2020 (U) Nandini et al. 2019 (U) Osredkar et al. 2023 (U) Piras et al. 2022 (U) Timperio et al. 2022 (U) Vernocchi et al. 2023 (F)	Needham et al. 2021 (F,P)
	Decreased in ASD patients	Adams et al. 2011 (F) El-Ansary et al. 2011 (P) Wang et al. 2020 (F,P)	/	/
	Levels comparable to neurotypical controls	Ha et al. 2021 (F); Laue, Bauer, et al. 2024 (F) Laue, Bonham, et al. 2024 (F) Wang et al. 2019 (F)	Kang et al. 2020 (F,P) Needham et al. 2021 (F,P) Turriziani et al. 2022 (U) L. Wang et al. 2012 (F)	Timperio et al. 2022 (U)
	Metabolite identified but not quantified		Daneberga et al. 2022 (U)	
	Levels of metabolite changing over time	Berding and Donovan 2020 (F)	/	/
Neuro-psychiatric correlates	Correlation of metabolite levels with ASD symptoms	Laue, Bauer, et al. 2024 (F)	Altieri et al. 2011 (U)	/
	Metabolite decrease associated with lower anxiety	/	Stewart Campbell et al. 2022 (U,F,P)	Stewart Campbell et al. 2022 (U,F,P)
Other clinical correlates	Higher metabolite levels associated with gastrointestinal (GI) symptoms	Laghi et al. 2021 (F)	Gabriele et al. 2016 (U)	/
	Change of metabolite levels in response to experimental treatment with improvement of ASD symptoms	Wang et al. 2020 (F,P)	Kang et al. 2020 (F,P); Stewart Campbell et al. 2022 (U,F,P)	Stewart Campbell et al. 2022 (U,F,P)
	Higher metabolite levels in younger ASD children	/	Altieri et al. 2011 (U) Gabriele et al. 2014 (U) Kang et al. 2018 (F)	/
	Higher metabolite levels in autistic females	/	Altieri et al. 2011 (U)	/
Data from metabolic disorders	Higher incidence of autistic features in patients with metabolic disorder involving metabolite	Cotrina et al. 2020 (P) Shchelochkov et al. 2024 (P,U) Witters et al. 2016 (P,U)	/	/

Note: Biological samples: F—feces; U—urines; P—plasma.

(El-Ansary et al. 2011). More recent studies found propionic acidemia associated with a much higher prevalence of autism (10/48, 21% in Cotrina et al. 2020; 12/31, 39% in Shchelochkov et al. 2024; and 5/8, 63% in Witters et al. 2016), and intellectual disability (ID) compared to the 1%–2% prevalence present in the general population. In summary, most results point toward elevated plasma and fecal levels of PPA as a risk factor for ASD, but conflicting findings suggest a more complex picture, in which metabolic dysregulation leading to either an accumulation or a decrease of PPA may have different outcomes depending on interindividual vulnerabilities which remain poorly understood.

3.1.2 | The Potential Role of Uremic Toxins in Autism Etiology

A greater consensus has been reached over the years around increased levels of p-cresol and p-CS in biological samples of ASD individuals. Of the 19 studies listed in Table 2, 14 reported significantly increased levels of p-cresol or p-CS in urine (Altieri et al. 2011; Chen et al. 2019; Gabriele et al. 2014, 2016; Gevi et al. 2020; Li et al. 2018; Mussap et al. 2020; Nandini et al. 2019; Osredkar et al. 2023; Piras et al. 2022; Timperio et al. 2022) or fecal samples (De Angelis et al. 2013; Kang et al. 2018; Vernocchi et al. 2023). Only two records did not discover any significant difference in urine levels of the uremic toxin (Daneberga et al. 2022; Turriziani et al. 2022). One of these, however, identified but did not quantify p-cresol in ASD urine samples (Daneberga et al. 2022). The second study contrasted p-cresol levels before and after gut mobilization in 25 young children with ASD, without collecting a specific control sample and only reports no difference between pre-treatment p-cresol levels in this newly-recruited ASD sample compared to previously-published control data from the same group (Turriziani et al. 2022). Finally, three studies reported comparable fecal concentrations of p-cresol in ASD and controls (Kang et al. 2020; Needham et al. 2021; Wang et al. 2012), but two of them still describe a non-significant trend toward p-cresol accumulation in ASD (Kang et al. 2020; Needham et al. 2021). Taken together, published results provide converging evidence supporting increased urinary p-cresol/p-CS as a possible biomarker for ASD.

Unfortunately, still too few ASD cohort studies exist on 4-EPS to draw firm conclusions. Only one record (Needham et al. 2021) analyzing plasma and stool samples from 130 and 57 ASD children, respectively, reported significantly higher levels of 4-EPS compared to control samples. A second study contrasting the urinary concentration of this metabolic compound between autistic individuals and their unaffected sibling reported only a non-significant increase among siblings with ASD (Timperio et al. 2022). However, the within-family design of the latter study may have reduced case–control differences and statistical power (Timperio et al. 2022). Nonetheless, the structural similarity between the biochemically related p-CS and 4-EPS, paired with these initial results, strongly encourages new research on this compound.

3.1.3 | Clinical Correlates of Altered Metabolic Profiles

Relatively few studies went beyond quantifying gut-derived metabolites in ASD bio-samples to characterize possible clinical correlations. The first study reporting higher levels of urinary p-cresol in ASD children (Altieri et al. 2011) also reported urinary p-cresol positively correlated with autism severity as measured by the Children Autism Rating Scales (CARS), for scores regarding use of body, verbal communication, and general impression. In addition, a significant p-cresol increase was reported in ASD children below 8 years of age and, among children in this age group, in females compared to males. Replicating these initial results in different biological samples, a second study found a significant negative correlation between fecal concentration of p-cresol and the age of ASD children (Kang et al. 2018). Recently, a large cohort study found fecal levels of SCFAs correlated with Social Responsiveness Scale (SRS-2) scores (Laue, Bauer, et al. 2024), indicating an association between PPA and the severity of autism-related behaviors in developing infants (6 weeks to 12 months old). These studies suggest that PPA and p-cresol may not only be correlated with autism per se, but rather with a more severe clinical presentation of ASD, especially earlier in life. Furthermore, higher fecal PPA concentrations were found associated with GI symptoms in ASD (Laghi et al. 2021). A similar correlation between chronic constipation and higher urinary p-cresol levels was reported by Gabriele et al. (2016). These findings seem to confirm that gut dysbiosis may play a significant role in GI dysfunction, but may also indicate that chronic constipation can influence the composition and metabolism of the gut microbiota.

3.1.4 | Effects of Experimental Treatments on Metabolite Levels and ASD Symptoms

A fascinating aspect emerging from recent studies is the impact that experimental treatments for GI symptoms in ASD children have on metabolite levels. An experimental intervention with probiotics and fructo-oligosaccharides aimed at improving gut dysbiosis in autistic individuals also had normalizing effects on SCFA levels, including PPA (Wang et al. 2020). Surprisingly, in this study pre-treatment fecal PPA was lower in ASD children compared to controls and increased following treatment. In a small open-label clinical trial of microbiota transfer, pre-treatment levels of p-CS displaying a slight non-significant increase in ASD individuals were indistinguishable from controls as a result of MTT, also resulting in a sizable improvement of GI symptoms (Kang et al. 2020). Finally, an experimental oral GI-restricted adsorbent (AB-2004) able to bind and sequester aromatic compounds through the GI tract was able to lower the levels of several microbiota-derived metabolites, including p-CS and 4-EPS, leading to an improvement in GI issues (Stewart Campbell et al. 2022).

Interestingly, all these therapeutic approaches also lead to improvement of ASD symptoms and/or decrease of anxiety levels in treated patients (Kang et al. 2020; Stewart Campbell et al. 2022; Wang et al. 2020). On the one hand, this association may indicate an interdependence between GI function and mental health, paving the path to possible pharmaceutical/nutraceutical treatments of ASD symptoms. On the other hand, gut mobilization in 21 chronically constipated young children 2.5–8 years old did significantly improve hyperactivity, anxiety, stereotypic behaviors, and autism severity, but trends in urinary p-cresol concentrations were not as uniform (Turriziani

et al. 2022), preventing oversimplistic views of the gut-brain axis in ASD.

3.2 | Cognitive and Behavioral Insights From Animal Models of Metabolite Exposure

A total of 47 records focused on animal models of PPA, p-cresol, and/or 4-EPS intoxication were selected (Table 3, with an extended version available as Suppl. Table S3). Out of these, the vast majority ($n = 36$) studied the effect of PPA or propionate neurotoxic doses in rodents. This is now a well-established chemical model of autism, as first investigations date back to 2007 (MacFabe et al. 2007). PPA effects have been tested in several different paradigms, such as adult, young, pre-, and postnatal exposure with both single and repeated administrations through oral, intravenous, and intraperitoneal routes. Regarding p-cresol and 4-EPS, the literature is more recent, and only eight and three studies have been conducted about animal exposure to these uremic toxins, respectively. Nevertheless, cognitive and behavioral features shared between these metabolites and the more established PPA model are already emerging (Table 3, Suppl Table S3).

3.2.1 | ASD Core Symptoms and Anxiety in Exposed Rodents and Insights From Other Animal Models of Autism

A significant reduction in social interests and behavior was consistently observed in animals exposed either to PPA (Abuaish et al. 2021; Benitah et al. 2023; Choi et al. 2018; Lobzhanidze et al. 2019, 2020; MacFabe et al. 2011; Shultz et al. 2008, 2015) or to p-cresol (Bermudez-Martin et al. 2021; Canaguier et al. 2025; Liu et al. 2022; Pascucci et al. 2020). Interestingly, this effect is clear in adult mice, yet a small but significant reduction in ultrasonic vocalization has been observed following perinatal exposure to p-cresol, but only in male pups (Canaguier et al. 2025). Increased repetitive/stereotyped behaviors, another core feature of ASD, were observed in rodents exposed to PPA (Foley, Ossenkopp, et al. 2014; MacFabe et al. 2007, 2010, 2011; Meeking et al. 2020; Thomas et al. 2012) and p-cresol (Bermudez-Martin et al. 2021; Canaguier et al. 2025; Pascucci et al. 2020; Tevzadze et al. 2018). On the other hand, evidence regarding 4-EPS is much weaker, as only one of the three studies performed administering 4-EPS demonstrated an increase in marble burying, a behavior associated with stereotypies and anxiety. Further research will be needed to confirm this initial observation.

Among frequent comorbid symptoms observed in humans with ASD, anxiety and hyperactivity were the most consistently induced by gut-derived metabolites in rodent models (Table 3). In particular, some evidence of increased anxiety-like behavior was reported in studies regarding all three metabolites (Alò et al. 2021; Benitah et al. 2023; Foley, Ossenkopp, et al. 2014; Hsiao et al. 2013; Liu et al. 2022; Needham et al. 2022; Pascucci et al. 2020; Stewart Campbell et al. 2022; Tevzadze et al. 2018). In addition, a GI-restricted adsorbent sequestering aromatic compounds in the gut demonstrated some efficacy in reverting anxiety-like behaviors both in a 4-EPS overproduction preclinical model (Stewart Campbell et al. 2022), and in a phase 1b/2a clinical trial (see par. 3.1.4). Similarly, most studies reported hyperactivity following treatment with PPA (Foley, MacFabe, et al. 2014; Lobzhanidze et al. 2020; MacFabe et al. 2007, 2008, 2010; Meeking et al. 2020; Mepham et al. 2021; Shultz et al. 2015; Thomas et al. 2012), although also the opposite effect was observed (Choi et al. 2018; Lobzhanidze et al. 2020; Morland et al. 2018). Studies on p-cresol are more limited and involve substantially different experimental designs. On the one hand, hyperactivity was observed following a single 1 mg/kg or 10 mg/kg i.p. injection of p-cresol to adult BTBR T + tf/J male mice (Pascucci et al. 2020) and following two weeks of repeated daily 35 mg/kg i.p. injections to C57BL/6J mice (Liu et al. 2022). Instead, a modest reduction in spontaneous activity was observed at postnatal day 12 (PD12) in C57BL/6J mice perinatally treated with p-cresol, while no effect was recorded later in adulthood (Canaguier et al. 2025). These results point toward substantial differences between acute behavioral effects and long-term developmental effects of p-cresol.

Finally, relevant insights about the involvement of gut-derived metabolites in ASD were also derived from other well-established animal models of ASD displaying altered levels of these compounds. PPA and 4-EPS concentrations were found to be increased in the stools of rats with valproate-induced autism-like behaviors (Kong et al. 2021), and in the blood of maternal immune activation and CNTNAP 2 mouse models of ASD (Hsiao et al. 2013; Needham et al. 2022). A recent study (Bertarini et al. 2025) found lower brain levels of p-cresol in the BTBR mouse model of ASD compared to CD-1 and C57BL/6J controls. These results raise interest in the relationship between peripheral and central concentrations of p-cresol, as well as differences between BTBR mice and other rodent models of ASD.

3.2.2 | Other Cognitive, Motor, and Neurological Anomalies in Exposed Animals

Several animal studies also focused on motor function and cognition (Table 3). Four records reported impairment in spatial memory and cognition, testified by lack of performance improvement in PPA-treated rats after training sessions in the Morris water maze (MWM) or T-maze (MacFabe et al. 2011; Mepham et al. 2019, 2021; Shultz et al. 2009). In one of these studies, fine motor coordination impairment was also recorded by evaluating the animals' ability to cross a narrow wooden beam (Shultz et al. 2009). Remarkably, Mepham et al. (2019) demonstrated significant improvement in rats after only 1 week of PPA discontinuation, suggesting that addressing higher PPA levels in autistic individuals may rapidly benefit their motor function. No motor evaluation was performed in 4-EPS animal models. This highlights a gap in the literature regarding the effects of uremic toxins on sensorimotor function, a field that certainly warrants further investigation.

In reference to learning and memory, female and male Sprague Dawley rats exposed to PPA (500 mg/kg sc.) twice daily between postnatal day 12 (P12) and P16, and tested after P29 displayed reduced discrimination in the novel object recognition test compared to controls (Alò et al. 2021). Instead, no acute effect on object recognition was observed following a single injection of 1 or 10 mg/kg p-cresol in BTBR mice (Pascucci et al. 2020).

TABLE 3 | Summary of core findings from animal models.

		Propionic acid (36 studies)	p-cresol (8 studies)	4-EPS (3 studies)
Cognitive, behavioral and neurological effects	Epileptic activity	MacFabe et al. 2007 ♂	/	/
	Impaired olfactory discrimination	Foley, MacFabe, et al. 2014 ♀♂ Sharma et al. 2024 ♂	/	/
	Decreased startle response	Foley et al. 2015 ♂; Kamen et al. 2019 ♂	/	/
	Increased startle response	Foley et al. 2015 ♀	/	Hsiao et al. 2013 *
	Low pre-pulse inhibition	Foley et al. 2015 ♂	/	/
	Decrease in social behavior	Abuaish et al. 2021 ♂ Benitah et al. 2023 ♀♂ Choi et al. 2018 ♂ Lobzhanidze et al. 2020 ♂, 2019 ♂ MacFabe et al. 2011 ♂ Shultz et al. 2015 ♂, 2008 ♂	Bermudez-Martin et al. 2021 ♂ Canaguier et al. 2025 ♀♂ Liu et al. 2022 * Pascucci et al. 2020 ♂	/
	Increase in restrictive/repetitive behavior	Foley, Ossenkopp, et al. 2014 ♀ MacFabe et al. 2011 ♂, MacFabe et al. 2010 ♂, MacFabe et al. 2007 ♂; Meeking et al. 2020 ♂ Thomas et al. 2012 *	Bermudez-Martin et al. 2021 ♂ Canaguier et al. 2025 ♀♂ Pascucci et al. 2020 ♂ Tevzadze et al. 2018 *	Needham et al. 2022 ♂
	Impairments in spatial cognition	MacFabe et al. 2011 ♂ Mepham et al. 2019 ♂, 2021 ♂ Shultz et al. 2009 ♂	/	/
	Memory impairments	Alò et al. 2021 *	/	/
	Increased locomotor activity (hyperactivity)	Foley, MacFabe, et al. 2014 ♂ Lobzhanidze et al. 2020 ♂ MacFabe et al. 2007 ♂, MacFabe et al. 2008 ♂, MacFabe et al. 2010 ♂. Meeking et al. 2020 ♂ Mepham et al. 2021 ♂ Shultz et al. 2015 ♂ Thomas et al. 2012 *	Liu et al. 2022 * Pascucci et al. 2020 ♂	/
	Decreased locomotor activity (hypoactivity)	Choi et al. 2018 ♂ Lobzhanidze et al. 2020 ♂ Morland et al. 2018 ♀	Canaguier et al. 2025 ♀♂	/

(Continues)

TABLE 3 | (Continued)

		Propionic acid (36 studies)	p-cresol (8 studies)	4-EPS (3 studies)
	Fine motor impairments	Shultz et al. 2009 ♀	/	/
	Reduced exploratory behavior	Alò et al. 2021 * Choi et al. 2018 ♂	/	/
	Increase in anxiety behavior	Alò et al. 2021 * Benitah et al. 2023 ♀♂ Foley, Ossenkopp, et al. 2014 ♀♂	Liu et al. 2022 * Pascucci et al. 2020 ♂ Tevzadze et al. 2018 *	Hsiao et al. 2013 * Needham et al. 2022 ♂ Stewart Campbell et al. 2022 ♂
	Signs of developmental delay at birth	Foley, Ossenkopp, et al. 2014 ♀♂ Sharma et al. 2024 ♂	/	/
	Recovery after discontinuation/treatment	Mepham et al. 2019 ♂	/	Stewart Campbell et al. 2022 ♂
Metabolite levels	Increase in ASD models	Kong et al. 2021 ♂	/	Hsiao et al. 2013 * Needham et al. 2022 ♂
	Decrease in ASD models	/	Bertarini et al. 2025 ♀♂	/
Neurobiology and brain differentiation	DNA damage in brain	El-Ansary et al. 2012 ♂, El-Ansary et al. 2013 ♂	/	/
	Decreased neuronal myelination	/	/	Needham et al. 2022 ♂
	Impaired oligodendrocyte maturation	/	/	Needham et al. 2022 ♂
	Increased astroglia markers	Choi et al. 2018 ♂ González-Cano et al. 2021 ♂ Lagod et al. 2024 ♀♂ Lobzhanidze et al. 2019 ♂ MacFabe et al. 2007 ♂, 2008 ♂, 2011 ♂ Shultz et al. 2008 ♂, 2009 ♂, 2015 ♂,	/	/
	Lower neuronal markers	Lagod et al. 2024 ♀♂ Lobzhanidze et al. 2019 ♂	/	/
	Altered neuronal transcription regulation	Al-Garni et al. 2025 ♂ Choi et al. 2018 ♂ MacFabe et al. 2007 ♂	Liu et al. 2022 *	/
	Altered expression of known ASD risk genes	Alò et al. 2021 * Lagod et al. 2024 ♀♂ Sharma et al. 2024 ♂	/	/

(Continues)

TABLE 3 | (Continued)

		Propionic acid (36 studies)	p-cresol (8 studies)	4-EPS (3 studies)
Neurotransmission	Altered synapse	Alò et al. 2021 * González-Cano et al. 2021 ♂ Lobzhanidze et al. 2019 ♂ Sharma et al. 2024 ♂ Zhvania et al. 2024 ♂	/	/
	Increased inhibition	Al-Garni et al. 2025 ♂ Kamalmaz et al. 2023 ♂ Morland et al. 2018 ♀	/	/
	Increased excitation/ excitotoxicity	Al-Suwailem et al. 2019 ♂ Bhat et al. 2016 ♂ Kamalmaz et al. 2023 ♀	Tevzadze et al. 2019 ♂, 2020*	/
	Altered glutamate receptors	/	Tevzadze et al. 2019 ♂, 2020*	/
	Altered dopamine signaling	Bhat et al. 2016 ♂	Bermudez-Martin et al. 2021 ♂ Pascucci et al. 2020 ♂	/
	Altered neurotransmission (other)	Al-Garni et al. 2025 ♂ Bhat et al. 2016 ♂	Tevzadze et al. 2018 ♂	/
Brain metabolism	Increase in oxidative stress and/or alterations in mitochondrial function	Abuaish et al. 2021 ♀ Al-Garni et al. 2025 ♂ El-Ansary et al. 2012 ♂ González-Cano et al. 2021 ♂ Kamalmaz et al. 2023 ♂ MacFabe et al. 2007 ♂, MacFabe et al. 2008 ♂, MacFabe et al. 2010 ♂ Sharma et al. 2024 ♂ Zhvania et al. 2024 ♂	/	/
	Altered glucose metabolism	Morland et al. 2018 ♀	/	/
	Altered lipid/phospholipid composition or phospholipase activation	Al-Dbass et al. 2021 ♂ El-Ansary and Al-Ayadhi 2014 ♂ El-Ansary et al. 2012 ♂ MacFabe et al. 2010 ♂ Thomas et al. 2012 *	/	/

(Continues)

TABLE 3 | (Continued)

		Propionic acid (36 studies)	p-cresol (8 studies)	4-EPS (3 studies)
	Increased neuroinflammation	Abuaish et al. 2021 ♀♂ Arafat and Shabaan 2020 ♂ Bhat et al. 2016 ♂ Choi et al. 2018 ♂ El-Ansary et al. 2012 ♂ González-Cano et al. 2021 ♂ Lagod et al. 2024 ♀♂ MacFabe et al. 2007 ♂, MacFabe et al. 2008 ♂, MacFabe et al. 2011 ♂; Sharma et al. 2024 ♂ Shultz et al. 2015 ♂, 2009 ♂, 2008 ♂	Liu et al. 2022 *	/
Other effects	Altered hormonal regulation	Abuaish et al. 2021 ♀	/	/
	Effects on other organs	Al-Dbass et al. 2021 ♀ Arafat and Shabaan 2020 ♂	/	/
Sex differences	No differences in the effect on female and male models	Benitah et al. 2023	Bertarini et al. 2025 Canaguier et al. 2025	/
	Differences in the effects on female and male models	Abuaish et al. 2021 Al-Suwailem et al. 2019 Foley et al. 2015 Foley, Ossenkopp, et al. 2014 Foley, MacFabe, et al. 2014 Kamalmaz et al. 2023	/	/

Note: Symbols: ♂ males only, ♀ females only, ♀♂ both males and females, *sex not specified.

Presumably, PPA and p-cresol may influence distinct cortical and subcortical regions involved in learning and memory. However, studies on prenatal PPA exposure also showed that the metabolite administered to Long-Evans rats from gestational day (GD) 12 to 16 produced only a delay in eye opening (Foley, Ossenkopp, et al. 2014), while a more prolonged exposure lasting from GD9 to GD15 resulted in a more severe developmental delay, with lower body weight at birth, impaired righting reflex and geotaxis (Sharma et al. 2024).

Finally, propionic acid was also shown to induce kindled limbic seizures in rats, though only in one study (MacFabe et al. 2007). Epilepsy is a common ASD comorbidity (Lord et al. 2020), and this dual effect of PPA in rodents, if confirmed, may be of great scientific and clinical relevance.

3.2.3 | Sexual Dimorphism in Behavioral Anomalies Caused by PPA Exposure

Several studies about PPA focused specifically on sexually dimorphic features of the ASD model, a highly relevant topic given the different prevalence and clinical manifestations of ASD in males and females (Ferri et al. 2018). Results in this regard, however, are still limited and their interpretation remains challenging. In 2014 and 2015, Foley et al. conducted a series of detailed evaluations on pre- and post-natally PPA and/or lipopolysaccharide (LPS)-exposed Long-Evans rats, laying the foundation for future investigations on the subject. In their initial study, prenatal PPA exposure produced subtle sex-related differences in open field motor function (higher total distance traveled, speed, and movement time in PPA-exposed males) and in social behavior (in the novel rat versus novel object test, PPA-exposed females spent more time in proximity with the novel rat) (Foley, MacFabe, et al. 2014). In their two following publications, the effects of pre- and post-natal exposure to PPA were evaluated, suggesting a double-hit model inducing repetitive behavior specifically in female rats (Foley, Ossenkopp, et al. 2014) and sensory hyper- and hypo-responsiveness in females and males, respectively (Foley et al. 2015).

More recent studies focused on the administration of PPA to young-adult rats and mice differ in treatment protocol and outcome. Two studies investigating PPA administered through the oral route found social impairment in PPA males but not in females (Abuaish et al. 2021), and greater cognitive defects with decreased learning and memory in PPA-treated male mice compared to females (Kamalmaz et al. 2023). The latter effects were accompanied by various sex-specific PPA-induced changes in immune, neurochemical, metabolic and oxidative stress (Kamalmaz et al. 2023) (Suppl. Table S3). Instead, a third study employing repeated i.p. injections of PPA (500 mg/kg) to adult Long Evans rats found males and females equally affected and did not record any influence of the estrous phase on the behavioral presentation (Benitah et al. 2023).

Regarding uremic toxins, only two very recent p-cresol studies analyzed differences between males and females. Bertarini et al. (2025) found no between-sex difference in naturally occurring p-cresol levels across different brain regions of several mouse strains, including BTBR. Canaguier et al. (2025) investigated the effects of pre- and post-natal exposure and detected no sex-related differences, except for a male-specific deficit in ultrasonic vocalizations recorded in newborns and lost during development (Canaguier et al. 2025). To our knowledge, no investigation has been carried out to investigate sex-specific effects of 4-EPS.

In summary, most studies suggest that females and males may interact differently with gut-derived metabolites, with females possibly protected by sex hormones, greater detoxification capacity, and higher glycolytic flux (Kamalmaz et al. 2023). Experimental designs largely differ in dose, administration schedule, developmental timing of exposure, species and strain. Predictably, these methodological differences largely influence sex-specific outcomes, likely explaining the few conflicting results on sexually dimorphic features of the PPA model. These is clearly insufficient information about sex-specific effects of uremic toxins (p-cresol and 4-EPS), and more research is needed in this direction.

3.3 | Neurobiological Effects of Gut-Derived Metabolites in Animal and Cellular Models

Several animal studies have investigated the mechanism of action underlying the behavioral and neurodevelopmental effects of gut-derived metabolites (Table 3). Additionally, a small number of in vitro studies using different cell models exposed to PPA, p-cresol, and 4-EPS have been recently published. A total of 10 records were retrieved using our search string, reporting findings from in vitro cellular studies, six assessing PPA, four assessing p-cresol, and one assessing 4-EPS. Data extracted from these studies is recapitulated in Table 4 (a detailed description of each study is available in Suppl. Table S4).

3.3.1 | Transcriptional Dysregulation and Impact on Mitotic Pathways

Several studies investigated the impact of gut-derived metabolites on the expression of neurodevelopmentally relevant gene pathways. Interestingly, a dysregulation in known ASD risk genes has been reported in both PPA-treated animal models and in cellular models exposed to all three microbiota-derived compounds. Genes implicated in ASD susceptibility by the largest exome sequencing study to date (Fu et al. 2022) whose expression was impacted by gut-metabolite exposure include *CHD8*, *SHANK2*, *SHANK3*, *PTEN*, *NIPBL*, and *NRXN1* (Alò et al. 2021; Guzmán-Salas et al. 2022; Lagod et al. 2024; Nankova et al. 2014; Sharma et al. 2024; Zheng et al. 2023). Remarkably, PTEN was downregulated in both PPA-treated mouse brains and exposed human neural stem cell (hNSC)-derived neurospheres (Abdelli et al. 2019; Lagod et al. 2024), as well as in BV2 mouse microglial cells cultured in media containing either p-cresol or 4-EPS (Zheng et al. 2023). Phosphatase and tensin homolog (*PTEN*) is a high-confidence ASD risk gene, and gene-disrupting variants in PTEN have been reported in up to 20% of children diagnosed with ASD and macrocephaly (Zheng et al. 2023). Therefore, these studies suggest direct effects of metabolite exposure on the expression of pivotal "autism

TABLE 4 | Summary of core findings from in vitro cellular models.

		Propionic acid (6 studies)	p-cresol (4 studies)	4-EPS (1 study)
Neural differentiation	Impaired neuronal differentiation	/	Guzmán-Salas et al. 2022 (h-Ne)	/
	Decreased neurite length	/	Guzmán-Salas et al. 2022 (h-Ne)	/
	Altered synaptic markers	/	Guzmán-Salas et al. 2022 (r-Ne)	/
	Decreased dendrite arborization	/	Guzmán-Salas et al. 2022 (r-Ne)	/
Gene expression	Altered expression of synaptic genes	Nankova et al. 2014 (r-O)	Guzmán-Salas et al. 2022 (r-Ne) Liu et al. 2022 (m-Ne)	/
	Altered expression of known ASD risk genes	Nankova et al. 2014 (r-O), Abdelli et al. 2019 (h-Ne, h-MG)	Guzmán-Salas et al. 2022 (r-Ne) Zheng et al. 2023 (m-MG)	Zheng et al. 2023 (m-MG)
	Altered transcription factors levels and/or activation	Nankova et al. 2014 (r-O)	Liu et al. 2022 (m-Ne)	/
Immune activation	Increased astroglial markers	Abdelli et al. 2019 (h-Ne, h-MG)	/	/
	Increased immune activation and inflammation	Abdelli et al. 2019, (h-Ne, h-MG)	/	/
	Decreased immune activation and inflammation	/	Zheng et al. 2022 & 2023 (m-MG)	Zheng et al. 2023 (m-MG)
Cell homeostasis	Altered mitotic pathways	Abdelli et al. 2019 (h-Ne, h-MG) Choi et al. 2020 (r-Ne) Nankova et al. 2014 (r-O)	Liu et al. 2022 (m-Ne) Zheng et al. 2023 (m-MG)	Zheng et al. 2023 (m-MG)
	Induction of pro-apoptotic pathways	/	Liu et al. 2022 (m-Ne)	/
Cell metabolism	Increase in oxidative stress and/or alterations in mitochondrial function	Buchanan et al. 2023 (h-Ne) Frye et al. 2016 & 2017 (h-AL) Nankova et al. 2014 (r-O)	Liu et al. 2022 (m-Ne)	/
	Altered lipid/phospholipid metabolism	Nankova et al. 2014 (r-O)	/	/

Note: Species: h-: human, m-: mouse, r-: rat. Cell type: Ne: neuronal primary cells or cell-lines; MG: microglial cell lines; AL: ASD individuals lymphoblastoid cells; O: other cell-lines.

genes". PTEN acts as a tumor suppressor, blocking the mTOR pathway, and also plays an important role in DNA damage repair (Wei et al. 2024). Interestingly, increased DNA damage has also been observed in the brain of PPA-treated hamsters and rats (El-Ansary et al. 2012, 2013).

Other relevant findings regarding the modulation of gene expression were reported. Nankova et al. conducted one of the most thorough evaluations of gene expression alterations induced by PPA, demonstrating induction of tyrosine hydroxylase (TH) by the SCFA in a cAMP response element binding

protein (CREB)-dependent manner and performing microarray transcriptomics to confirm activation of other pathways downstream of CREB. Besides the altered regulation of ASD genes, they identified modifications in the expression of several synaptic genes, transcriptional regulators, genes involved in the dopamine and serotonin pathways, and genes associated with cellular energy production and metabolism (Nankova et al. 2014). This strengthened earlier results from mouse models, indicating increased phospho-CREB immunoreactivity in the hippocampus and white matter resulting from PPA exposure (MacFabe et al. 2007). Interestingly, these results already highlight a convergence in regulatory pathways, as CREB is located downstream of the PTEN/AKT mitogenic pathway (Dinevska et al. 2024). In addition, PPA was also reported to induce the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway (Choi et al. 2018) and to increase mTOR levels (Al-Garni et al. 2025), both upstream of CREB activation and downstream to reduced PTEN expression.

The involvement of uremic toxins in mitotic pathways, on the other hand, appears complex and cell-specific. On the one hand, p-cresol and 4-EPS induce the downregulation of tumor suppressor genes like PTEN in mouse microglial cells (Zheng et al. 2023). In addition to blunting innate immune responses (Zheng et al. 2022, 2023), this effect may also influence microglial-mediated synaptic pruning, although this modulation of neuronal connectivity remains to be demonstrated. On the other hand, p-cresol represses cell cycle-associated genes and induces pro-apoptotic pathways in primary mouse hippocampal neurons (Liu et al. 2022), conceivably affecting cognitive functions like learning and memory.

3.3.2 | Effects on Brain Composition and Neurotransmission

Animal studies have consistently reported PPA-induced increases in astroglial markers, especially glial fibrillary acidic protein (GFAP), possibly accompanied by a concomitant decrease in the neuronal population, signified by a lower GFAP/β-III-tubulin ratio (Choi et al. 2018; González-Cano et al. 2021; Lagod et al. 2024; Lobzhanidze et al. 2019; MacFabe et al. 2007, 2008, 2011; Shultz et al. 2008, 2009, 2015). These findings received in vitro confirmation by a recent study reporting a GFAP-positive specific cell growth in hNSC-derived neurospheres (Abdelli et al. 2019). Hence PPA exposure during development may shift brain cellular composition toward an astrocyte-neuronal population imbalance. Similar changes in brain cell composition were not reported for p-cresol animal models to this date, possibly pointing toward either a different mechanism of action or, more likely, a gap in current knowledge, given the confirmed activation of mitotic gene pathways by uremic toxins in mouse microglia (Zheng et al. 2023). Importantly, germ-free mice colonized with 4-EPS+ engineered bacteria display an increase in Notch signaling, associated with over-proliferation of immature oligodendrocytes, impaired oligodendrocyte maturation, and reduced axon myelination (Needham et al. 2022), demonstrating a considerable impact of 4-EPS on this glial subpopulation and encouraging further studies regarding the functional consequences of these effects on neuronal connectivity and information processing.

Several animal studies also demonstrated that gut metabolites interfere with neurotransmission. PPA was found to impact synapse formation (Alò et al. 2021; González-Cano et al. 2021; Lobzhanidze et al. 2019; Sharma et al. 2024; Zhvania et al. 2024), to affect monoaminergic neurotransmissions (i.e., dopamine, serotonin and norepinephrine), and to promote excitation/inhibition (E/I) imbalance and excitotoxicity (Al-Garni et al. 2025; Al-Suwailem et al. 2019; Bhat et al. 2016; Kamalmaz et al. 2023; Morland et al. 2018). Similar findings were reported for p-cresol, which was found to increase levels of N-methyl-D-aspartate (NMDA) receptor and to affect its subunit composition (Tevzadze et al. 2019, 2020). P-cresol effects on dopaminergic neurotransmission appear more complex: it enhances tissue levels of dopamine and its metabolites in the amygdala, caudate putamen and nucleus accumbens of BTBR mice (Pascucci et al. 2020), an effect compatible with the inhibition of dopamine-β-hydroxylase (Goodhart et al. 1987) and relevant to the behavioral abnormalities observed in this mouse model of ASD (Pascucci et al. 2020). At the same time, it reduces dopamine release from mesolimbic neurons reaching the n. accumbens from the ventral tegmental area, an effect which may contribute to reduced social reward (Bermudez-Martin et al. 2021). Interestingly, nasally administered oxytocin rescued the increased anxiety and repetitive behavior in p-cresol-treated mice by stimulating a different but converging social reward circuitry (Tevzadze et al. 2018). Finally, another effect of p-cresol potentially important for neurodevelopment is represented by its interference with neuronal differentiation and neurite elongation observed in neuro2a cells, as well as an impairment of dendrite arborization with concomitant decrease in pre−/post-synaptic markers observed in rat primary hippocampal neurons (Guzmán-Salas et al. 2022).

The existing literature regarding 4-EPS effects on brain function is currently limited to its previously discussed negative modulation of oligodendrocyte maturation, yielding reduced axon myelination correlated with anxiety-like behaviors in mice (Needham et al. 2022). Whether and to what extent this phenomenon differentially affects brain neurotransmissions remains to be elucidated.

3.3.3 | Oxidative Stress and Brain Metabolism

Converging evidence supports the disruption of energy production and increased oxidative stress as playing a role in gut-metabolites-mediated neurotoxicity, especially for PPA and p-cresol (Table 4). PPA has been shown to impact neuronal metabolism in two main ways: promoting oxidative stress by altering mitochondrial homeostasis and function (Abuaish et al. 2021; Al-Garni et al. 2025; Buchanan et al. 2023; El-Ansary et al. 2012; Frye et al. 2016, 2017; González-Cano et al. 2021; Kamalmaz et al. 2023; MacFabe et al. 2007, 2008, 2010; Nankova et al. 2014; Sharma et al. 2024; Zhvania et al. 2024), and impacting lipid and phospholipid metabolism and therefore neural membranes' lipid composition (Al-Dbass et al. 2021; El-Ansary et al. 2012; El-Ansary and Al-Ayadhi 2014; MacFabe et al. 2010; Nankova et al. 2014; Thomas et al. 2012).

Studies focusing on mitochondria showed PPA produced changes in their number, dimensions, and membrane phospholipid composition (Buchanan et al. 2023; Lobzhanidze

et al. 2020; MacFabe et al. 2010; Zhvania et al. 2024), as well as transcriptional dysregulation of several genes involved in mitochondrial functions (Nankova et al. 2014). Increases in lipid peroxidation byproducts, like malondialdehyde, and in catalase, glutathione (GSH), and glutathione peroxidase (GPX) were also consistently reported (El-Ansary et al. 2012; MacFabe et al. 2007, 2008; Sharma et al. 2024). In addition, two studies analyzing lymphoblastoid cell lines (LCLs) from ASD individuals with normal versus elevated oxidative/mitochondrial serum parameters reported greater detrimental effect exerted by PPA on LCLs from the latter group, with an already compromised mitochondrial function (Frye et al. 2016, 2017).

Emerging evidence indicates that also p-cresol increases oxidative stress and disrupts brain mitochondrial dysfunction, as its exposure enhanced the expression of mitofusion-associated genes in primary hippocampal mouse neurons (Liu et al. 2022; Renaldi, Wiguna, et al. 2025). Furthermore, p-cresol and/or pCS consistently increased oxidative stress in several distinct animal and cellular models (Renaldi, Wiguna, et al. 2025). Collectively, these results spur interest into therapeutic strategies involving prebiotics or probiotics to reduce oxidative stress and improve behavior by correcting gut dysbiosis and by reducing the production and absorption of neuroactive gut-derived compounds (Renaldi, Persico, et al. 2025).

Instead, lipid and phospholipid metabolism shifts seem to be specific to PPA. In rodents, PPA was shown to increase phospholipase A2 activity (Al-Dbass et al. 2021) and to decrease plasmalogens, glycerophospholipids able to prevent polyunsaturates oxidation, in brain membranes (MacFabe et al. 2010). This change in lipid/phospholipid neuronal membrane composition seemingly reflects a similar pattern found in the blood of ASD individuals (El-Ansary et al. 2012; El-Ansary and Al-Ayadhi 2014; MacFabe et al. 2010; Thomas et al. 2012).

3.3.4 | Immune Modulation and Neuroinflammation in Models of Metabolites Exposure

The last mechanism that emerged from animal and cellular models of PPA, p-cresol, and 4-EPS exposure was the participation of gut-derived metabolites in immune modulation and neuroinflammation. The increased microglial population in PPA-treated animal models already presented in Section 3.3.2 represents a first indication of immune activation in the brain. In addition, numerous studies identified a PPA-mediated increase in pro-inflammatory cytokines, especially IL-6 and TNF-α, mostly in the brain but also in the lungs of treated animals (Abdelli et al. 2019; Arafat and Shabaan 2020; Bhat et al. 2016; Choi et al. 2018; Lagod et al. 2024). While PPA consistently enhances neuroinflammation in numerous animal and cellular models (Abdelli et al. 2019; Abuaish et al. 2021; Bhat et al. 2016; Choi et al. 2018; El-Ansary and Al-Ayadhi 2014; Frye et al. 2017; González-Cano et al. 2021; Lagod et al. 2024; MacFabe et al. 2007, 2008, 2011; Sharma et al. 2024; Shultz et al. 2008, 2009, 2015), fewer studies have investigated p-cresol ad 4-EPS, yielding results which appear less consistent. On the one hand, p-cresol ad 4-EPS seemingly attenuate LPS-mediated activation of BV2 mouse microglia in vitro (Zheng et al. 2022, 2023). This may be consistent with the model proposed by Needham et al., suggesting that 4-EPS-mediated induction of notch pathways leads to an increase in numbers but a decrease in differentiation of mouse microglia (Needham et al. 2022). On the other hand, especially for p-cresol-derived p-CS also pro-inflammatory effects have been reported, at least in endothelial cells, and these effects would be more compatible with the increase in oxidative stress produced by p-cresol and p-CS. Results on p-cresol/p-CS and on 4-EPS are still limited and linking effects on microglia with the broader scenario on neuroinflammation will require further research.

4 | Discussion and Conclusions

Despite ASD's high heritability, genetics alone can hardly explain phenomena like the discordance in clinical presentation between ASD monozygotic twins (Myers et al. 2021) or the phenotypic heterogeneity in autistic individuals carrying the same recurrent pathogenic variant (Loureiro et al. 2021). Therefore, for the majority of patients ASD is currently viewed as the result of complex gene–gene and gene–environment interactions, often involving *de novo* and inherited rare variants with incomplete penetrance, common predisposing variants present in their genetic background, and the exposure to environmental risk factors able to modulate the phenotype. This has already been proven for several risk factors, most conclusively for advanced parental age at conception and perinatal brain damage due to neonatal hypoxia (Lord et al. 2020).

Given the emerging role of the gut-brain axis in psychiatry, the present review aimed to address whether the gut-microbiota, and especially known neurotoxic microbial metabolites, could contribute to the pathogenesis of ASD and to summarize current knowledge on possible neurobiological mechanisms. An overview of the potential role of propionic acid, p-cresol/p-CS, and 4-ethylphenyl sulfate in autism susceptibility is displayed in Figure 3.

The first gut-derived metabolite to be investigated in autism research was PPA (MacFabe et al. 2007), a pleiotropic microbial metabolite generated by a vast array of intestinal microbes through the fermentation of undigested sugars, the breakdown of proteins, and the crossfeeding on the fermentation products of other colonic microbes (Louis and Flint 2017). Like other SCFAs, PPA exerts beneficial effects on human health at multiple levels, including immune modulation, metabolism, and mucosal homeostasis. At physiological concentrations generated in the colon, propionate acts through G-protein coupled receptors FFAR2 (GPR43) and FFAR3 (GPR41), modulating enteroendocrine hormone release (GLP-1, PYY), intestinal gluconeogenesis, and gut–brain neural circuits that improve glucose homeostasis, appetite regulation and energy balance (Lee et al. 2024; Facchin et al. 2025; Han et al. 2024). Propionate also participates in hepatic anaplerosis via conversion to propionyl-CoA and entry into the TCA cycle; it exerts a hypocholesterolemic effect by competing with acetate in cholesterol metabolism, and exerts anti-inflammatory and immunomodulatory actions on myeloid and epithelial cells (including modulation of dendritic cell maturation and cytokine profiles). These mechanisms plausibly explain its

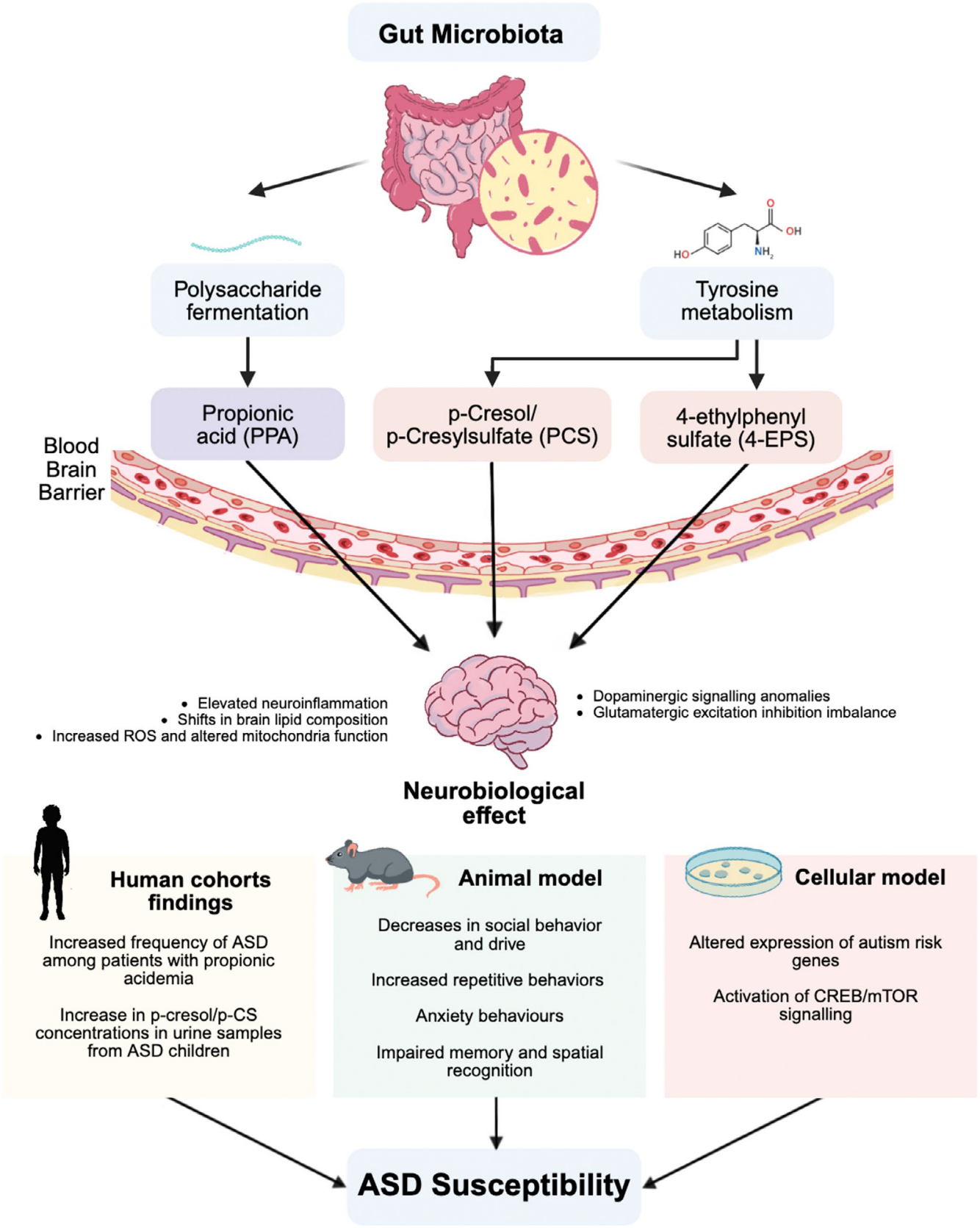

FIGURE 3 | Summary overview. The role of microbiota metabolites propionic acid, p-cresol, and 4-ethylphenyl sulfate in autism susceptibility.

demonstrated benefits in metabolic and inflammatory disease models, as well as in human trials testing targeted colonic delivery of propionate esters.

Meanwhile, the literature analyzed in this systematic review shows that neurotoxic doses of propionate can be harmful to neurodevelopment. Animal and cellular models exposed to

high doses of propionic acid reproduce a spectrum of changes overlapping with autism-relevant biology: microglial activation and astrogliosis, neuroinflammatory cytokine induction, oxidative stress and mitochondrial alterations, shifts in brain lipid and phospholipid composition, transcriptional dysregulation of neurodevelopmental genes (including changes in PTEN/AKT/mTOR and CREB signaling) (Table 4). Rodent models display behavioral phenotypes reminiscent of core human ASD symptoms, including decreased social behavior and drive, paired with increased repetitive behaviors and sensory anomalies (Table 3). Anxiety behaviors, impaired memory and spatial cognition, and either hypo- or hyperactivity in PPA-intoxicated rodents (Table 3) mimic clinical features often comorbid with human ASD. Importantly, clinical observations from patient cohorts affected by propionic acidemia, a rare autosomal recessive genetic disorder of propionyl-CoA metabolism, further support that chronic supra-physiological accumulation of propionate and related metabolites is associated with higher rates of neurodevelopmental impairment and autism (Cotrina et al. 2020; Shchelochkov et al. 2024; Witters et al. 2016). However, human cohort studies find fecal/plasma propionate levels either elevated, comparable, or decreased in ASD compared to neurotypical controls (Table 2). Hence, elevated propionate is not a universal finding in ASD.

Reconciling these apparently contradictory lines of evidence likely requires a dose- and context-dependent model. At physiological concentrations and within the intact metabolic capacity of the host, propionate acts as a beneficial signaling metabolite. In contrast, supra-physiological exposure (acute high doses in experimental models or chronic systemic accumulation as occurs in metabolic disorders like PA) may produce the mitochondrial stress, epigenetic and transcriptional dysregulation, and neuroinflammation promoting autism pathophysiology. Finally, genetic background likely modifies susceptibility: vulnerability conferred by rare or even by common variants located in genes that regulate mitochondrial function, detoxification, or neurodevelopmental pathways may convert an otherwise benign increase in propionate into a pathophysiological insult. Therefore, while propionate has been recommended as a therapeutic or nutritional target in several metabolic and inflammatory conditions, caution is warranted when extrapolating benefit to populations at risk for impaired propionate handling or harboring genetic variants that enhance ASD risk. Future work should quantify exposure thresholds, map host genotypes that confer vulnerability, and measure systemic (not just fecal) propionate alongside functional readouts (mitochondrial markers, PTEN/mTOR signaling, microglial activation) in well-phenotyped human cohorts.

The two chemically related uremic toxins p-cresol/p-CS and 4-EPS have been investigated to a very different extent, much more the former than the latter (Tables 2–4). An increase in p-cresol/p-CS concentrations in urine samples from autistic children has been reported by 14 of the 19 human studies reviewed (Altieri et al. 2011; Chen et al. 2019; De Angelis et al. 2013; Gabriele et al. 2014, 2016; Gevi et al. 2020; Kang et al. 2018; Li et al. 2018; Mussap et al. 2020; Nandini et al. 2019; Osredkar et al. 2023; Piras et al. 2022; Timperio et al. 2022; Vernocchi et al. 2023) (Table 2). This striking concordance strongly supports an association between this uremic toxin and ASD, to the point that urinary p-cresol/p-CS has been proposed as a potential biomarker (Basra et al. 2025). This association does not necessarily imply a causal role, but the growing number of studies demonstrating the induction of ASD core symptoms like social impairment and stereotypic behaviors as well as hyperactivity and anxiety, in p-cresol or p-CS-treated animals is beginning to provide convergent support to the potential for pathogenic or at least pathomorphic roles, modulating autism severity (Bermudez-Martin et al. 2021; Liu et al. 2022; Pascucci et al. 2020; Tevzadze et al. 2018). Moreover, increased oxidative stress and inflammation may represent a common pathogenic mechanism shared by PPA and p-cresol/p-CS (Liu et al. 2022; Renaldi, Wiguna, et al. 2025).

Animal studies also demonstrated that p-cresol/p-CS and 4-EPS impact glutamatergic and dopaminergic signaling (Al-Suwailem et al. 2019; Bermudez-Martin et al. 2021; Bhat et al. 2016; Kamalmaz et al. 2023; Tevzadze et al. 2019, 2020). Glutamatergic signaling anomalies are central to the so-called excitation/inhibition (E/I) imbalance theory of autism (Rubenstein and Merzenich 2003). This theory identifies a disproportion between glutamatergic and GABAergic signaling as one of the leading causes of network dysregulation in the autistic CNS and has gained credit in the last 20 years, especially given the renowned co-occurrence of autism and epilepsy, also caused by E/I imbalance, and the numerous genes that emerged from genomic studies of ASD which are functionally involved in the maintenance of E/I stability. Therefore, the disruption of this balance mediated by gut-derived metabolites also supports their involvement in autism pathogenesis. Finally, dopaminergic signaling anomalies described in p-cresol/p-CS-treated animals are also very relevant, because of their brain-region specificity and behavioral correlates (Bermudez-Martin et al. 2021; Pascucci et al. 2020), possibly linking p-cresol/p-CS not only to ASD but also to ADHD and anxiety, two among the most frequently occurring behavioral conditions co-occurring with ASD (DiCarlo and Wallace 2022).

Despite their biochemical and mechanistic specificites, behavioral and neurobiological effects shared by PPA, p-cresol/p-CS and 4-EPS are beginning to emerge from animal and cellular models. From a behavioral standpoint, all three metabolites induced stereotypic behaviors, reduced social interactions, and anxiety-like behaviors in exposed rodents (Table 3). While there are known sensory and cognitive contributors to anxiety disorders in autistic individuals, like atypical sensory processing, alexithymia (i.e., difficulties in understanding and labeling emotions), and "intolerance of uncertainty" (South and Rodgers 2017), a dysbiosis-induced accumulation of these neurotoxins in the bloodstream and CNS of ASD children, could also contribute to intensify baseline levels of anxiety, leading to a higher susceptibility to external and internal triggers.

Furthermore, another biological modulation broadly shared by all three compounds, at least in in vitro models, is exerted on the expression of known autism genes (par. 3.3.1 and Table 4). For example, initial results point toward an inhibition of PTEN and therefore on the downstream activation of mTOR and CREB signaling, possibly exerted both by PPA and by p-cresol/p-CS both in vitro and in vivo (Abdelli et al. 2019; Al-Garni et al. 2025; Lagod et al. 2024; MacFabe et al. 2007; Nankova et al. 2014;

Zheng et al. 2023). Transcriptional and post-transcriptional modulation of critical autism genes and/or of autism-related gene pathways is a very promising future avenue of investigation. However, these results should be interpreted with caution at this stage, because the effect of each metabolite on autism gene expression may largely differ depending on cell type and most studies have been performed on microglia, providing more information on neuroinflammation and oxidative stress than on neurodevelopment (Table 4).

This article has at least two main limitations, which must be duly acknowledged. First, much evidence reviewed here stems from animal models, which provide information not necessarily applicable to humans with ASD. The purpose of this study was to give a comprehensive overview of the potential role of three functionally-relevant gut microbiota metabolites in ASD susceptibility. Therefore, all sources of evidence were collected, indeed without overlooking animal models which have provided a substantial amount of currently available evidence, in some instances even preceding findings in human cohorts. However, there is substantial heterogeneity among animal models, with differences in microbiota profiles and behavioral outcomes driven by confounding factors such as sex, age, housing, and diet, which often reduce reproducibility. Moreover, animal models may not fully capture the genetic, environmental, and developmental complexity of human ASD, limiting direct clinical translation. Finally, while differences in animal behavior between test and control animals can be highly informative of the effect of a given metabolite on brain physiology, the translation from animal to human behavior may often be less obvious or fully understood, adding another layer of complexity to the validity of their results. Hence, evidence derived from human and animal studies should never be viewed as equivalent, but rather as complementary. Second, evidence of contributions to ASD susceptibility appears at this stage convincing for PPA, sufficient for p-cresol/p-CS, and still very limited for 4-EPS. The scientific quality and the heuristic potential of studies investigating 4-EPS suggested its inclusion in the present work, which we hope will spur further investigations on this intriguing metabolite. Nonetheless, reaching the critical mass of scientific evidence needed to conclusively demonstrate a functional contribution by 4-EPS to ASD susceptibility is still "work in progress".

In conclusion, our systematic review found much evidence supporting the involvement of these gut-derived metabolites in autism susceptibility, both from human cohort studies and experimental in vitro and in vivo models, albeit to a different extent. Increased levels of the three metabolic compounds have been reported in the majority of ASD cohorts analyzed to date (Table 2). In addition, the induction of behaviors resembling human core ASD symptoms and frequent co-morbid disturbances in animal models (Table 3) lends further support to a phenotypically coherent modulation of behavior and underlying neural circuits mediated by these metabolic compounds. Neurochemical and metabolic mechanisms at least partly overlapping among these three metabolites may include the modulation of glutamatergic and dopaminergic neurotransmission, as well as metabolic effects on mitochondrial function, oxidative stress, and skewed expression of established ASD susceptibility genes. Further research will be needed to elucidate the role of transcriptional dysregulation on the neurodevelopmental and neurotoxic effects of PPA, p-cresol/p-CS, and 4-EPS, as well as in microglia proliferation/differentiation and mitochondrial homeostasis. Finally, the identification of potential therapeutic approaches addressing both altered metabolite levels and clinical symptoms and comorbidities urges further developments in the field, hopefully leading to an improved quality of life for autistic individuals.

Author Contributions

Laura Sandoni: writing – original draft, conceptualization, methodology, study screening and selection, data extraction. **Lisa Asta:** writing – review and editing, methodology, study screening and selection, data extraction. **Nicole Giompaolo:** writing – review and editing, data extraction. **Rinvil Renaldi:** writing – review and editing, conceptualization, validation. **Alberto Amaretti:** writing – review and editing, conceptualization, validation. **Maddalena Rossi:** writing – review and editing, conceptualization, validation. **Antonio M. Persico:** writing – review and editing, supervision, conceptualization, methodology, validation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing does not apply to this article, as no datasets were generated in the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** List of the 411 records screened (duplicate records were removed from this list). **Table S2:** Data mining of articles reporting findings on propionic acid (PPA), p-cresol and 4-ethylphenyl sulfate (4-EPS) involvement in autism from human cohorts. **Table S3:** Data mining of articles reporting findings from animal models of propionic acid (PPA), p-cresol and 4-ethylphenyl sulfate (4-EPS) intoxication and/or other ASD models with non-physiological levels of PPA, p-cresol or 4-EPS. **Table S4:** Data mining of articles reporting findings from cell models of propionic acid (PPA), p-cresol and 4-ethylphenyl sulfate (4-EPS) exposure.