

Table SI. Key evidence for synergistic and antagonistic crosstalk between SCFAs and tryptophan microbial metabolites in HDP pathogenesis.

First author, year	Metabolite class	Mechanism/pathway	Interaction type	Study model	Key findings	(Ref.)
Beckers <i>et al</i> , 2025	SCFAs + microbiome	Coordinated dysregulation of microbiome-metabolome axis	Shared regulatory networks	BPH/5 mouse model (superimposed preeclampsia)	Pregnancy-specific shifts in maternal microbiome and metabolome with notable alterations in SCFA profiles accompanied by changes in microbial community structure	(61)
Wei <i>et al</i> , 2025	Tryptophan metabolites	AhR activation	Shared regulatory hub	sFlt-1-induced preeclampsia mouse model	Indole-3-lactic acid alleviates preeclampsia-like phenotypes	(17)
Wei <i>et al</i> , 2025	Tryptophan metabolites	AhR/VCAN pathway	Shared regulatory networks	Trophoblast cell lines (HTR-8/SVneo)	Indole-3-lactic acid promotes trophoblast migration and invasion	(18)
Jin <i>et al</i> , 2022	SCFAs (butyrate)	GPR43-mediated signaling	Shared regulatory networks	Gut dysbiosis mouse model + macrophage/trophoblast co-culture	Butyrate modulates macrophage polarization toward anti-inflammatory M2 phenotype and enhances trophoblast invasive capacity	(55)
Li <i>et al</i> , 2022	SCFAs	Diagnostic biomarker potential	Synergistic protective effects	Clinical cohort (preeclamptic vs. healthy pregnant women)	Circulating acetate and butyrate levels distinguish patients with preeclampsia from healthy controls (AUC ≤ 1.00)	(52)
Marić <i>et al</i> , 2022	SCFAs + tryptophan metabolites	Multi-omics integration	Combined predictive value	Multi-omics analysis of preeclampsia cohort	Tryptophan metabolites contribute notably to integrative signatures identifying women at risk; combination with clinical variables improves predictive accuracy	(95)
Cao <i>et al</i> , 2025	SCFAs + tryptophan metabolites	Metabolite-based risk stratification	Combined predictive value	Large-scale prospective serum metabolomic profiling in patients with suspected preeclampsia	Candidate predictive biomarkers identified from both metabolite classes	(97)
Xu <i>et al</i> , 2025	SCFAs + tryptophan metabolites	Compensatory metabolic regulation	Antagonistic/compensatory	Rat model of preeclampsia	Extensive metabolic remodeling across multiple compartments involving both metabolite classes	(101)

Yutao <i>et al</i> , 2026	SCFAs + tryptophan metabolites	Multi-pathway modulation	Antagonistic/compensatory	Metabolomic profiling in preeclampsia model	Therapeutic interventions (aspirin) simultaneously modulate multiple metabolic pathways including SCFA and tryptophan metabolism	(102)
Jääskeläinen <i>et al</i> , 2018	Tryptophan metabolites	Coordinated metabolic shifts	Antagonistic/compensatory	Cord blood plasma from preeclamptic infants	Elevated levels of carnitine precursors and trimethylated compounds alongside tryptophan-associated metabolites	(73)
Ferranti <i>et al</i> , 2020	SCFAs + tryptophan metabolites	Gene-environment interactions	Dietary/genetic modulation	Early pregnancy serum from African American women	Both SCFA-associated and tryptophan pathway metabolites identified among discriminating features for HDP	(74)
Luo <i>et al</i> , 2023	Tryptophan metabolites (AhR)	Hormonal-metabolic crosstalk	Dietary/genetic modulation	Human decidualization model	hCG-stimulated IL4I1 promotes human decidualization via AhR, revealing hormonal association with tryptophan metabolism that may interact with SCFA signaling	(103)
Escorcía Mora <i>et al</i> , 2025	Gut microbiota	Endometrial-microbiota axis	Combined predictive value	Review on female reproductive health	Endometrial signaling pathways may be influenced by microbial metabolites, including SCFAs and tryptophan derivatives	(105)
Song <i>et al</i> , 2024	Adenosine signaling	Metabolic integration nodes	Combined predictive value	Trophoblast cell line (HTR-8/SVneo)	CD73/adenosine signaling pathway reveals complex interactions that could serve as nodes for metabolite integration	(106)

AhR, aryl hydrocarbon receptor; AUC, area under the curve; BPH/5, blood pressure high/5 (mouse model of superimposed preeclampsia); GPR43, G protein-coupled receptor 43; hCG, human chorionic gonadotropin; HDP, hypertensive disorders of pregnancy; IL4I1, IL-4-induced-1; SCFAs, short-chain fatty acids; sFlt-1, soluble fms-like tyrosine kinase-1; VCAN, versican.

Table SII. Summary of clinical translation approaches targeting SCFAs and tryptophan microbial metabolites in HDP.

First author, year	Category	Study model	Intervention/target	Key findings	Clinical implication	(Ref.)
Chang <i>et al</i> , 2020	Biomarkers	Human case-control	Fecal SCFAs (butyrate and propionate)	Reduced fecal SCFAs in preeclamptic women	Non-invasive diagnostic potential	(50)
Powell <i>et al</i> , 2018	Biomarkers	Human case-control	Serum metabolic profiling	Utility of metabolic profiling in diagnosing pregnancy complications	Integration of multiple metabolite classes	(107)
Schwartz <i>et al</i> , 2025	Dietary intervention	Human observational	Dietary fiber intake	Fiber intake was associated with gut bacterial diversity and SCFA production	Potential nutritional foundation for SCFA-mediated effects	(62)
Gomez-Arango <i>et al</i> , 2016	Dietary intervention	Human cohort	Early pregnancy diet	Increased BP was associated with reduced butyrate production	Dietary strategies to enhance butyrate production	(109)
Fan <i>et al</i> , 2026	Dietary intervention	BPH/5 mouse model	Monitored food intake	Early pregnancy diet modulated maternal microbiome and SCFA pathways	Dietary interventions modify SCFA-associated pathways	(64)
Wu <i>et al</i> , 2020	Dietary intervention	Review	Dietary nutrients	Dietary nutrients mediated intestinal host defense peptide expression	Nutritional modulation of immune-associated pathways	(110)
Whitmore <i>et al</i> , 2024	Dietary intervention	Review	Nutritional modulation	Host defense peptide synthesis as a host-directed therapeutic strategy	Implications for pregnancy-associated inflammation	(111)
Wang <i>et al</i> , 2023	Microbiome-targeted approach	Human RCT	Lean red meat addition to a vegetarian diet	Dietary pattern modulated gut microbiota composition	Proof-of-concept in reshaping microbial communities	(112)
Liu <i>et al</i> , 2017	Microbiome-targeted approach	IPEC-J2 cells and piglets	<i>Lactobacillus reuteri</i> I5007	Probiotic modulated intestinal host defense peptide expression	Probiotic supplementation may influence immune pathways	(113)
Xiong <i>et al</i> , 2016	Microbiome-targeted approach	Piglets	Butyrate supplementation	Butyrate upregulated host defense peptides via HDAC inhibition	Mechanistic support for SCFA-based interventions	(96)
Zong <i>et al</i> , 2023	Microbiome-targeted approach	Review	Microbiome-targeted treatments	Comprehensive review of microbiome changes and treatments in PE	Potential for microbiome-based therapies	(114)
Lu <i>et al</i> , 2025	Targeted therapy	Rat model	SCFA supplementation	SCFA supplementation reduced cathepsin C levels and alleviated PE symptoms	Gut microbiota-SCFAs-cathepsin C pathway as a therapeutic target	(56)
Yong <i>et al</i> , 2022	Targeted therapy	Rat model	Sodium butyrate	Sodium butyrate alleviated hypertensive and proteinuric	SCFA supplementation improves gut microbiota and metabolite	(58)

Ishimwe <i>et al</i> , 2022	Targeted therapy	Dahl salt-sensitive rat	1,3-Butanediol	phenotypes Periconceptual supplementation suppressed PE-like phenotype	production Metabolic interventions targeting SCFA pathways	(59)
Zhao <i>et al</i> , 2025	Targeted therapy	Rat model	Endogenous AhR ligand	AhR ligand induced PE-like phenotypes; dysregulated pathways represent therapeutic targets	AhR pathway as therapeutic target	(78)
Santillan <i>et al</i> , 2015	Targeted therapy	IDO knockout mouse	IDO deficiency	IDO-deficient mice develop glomerular endotheliosis, proteinuria, gestational endothelial dysfunction and fetal growth restriction, recapitulating human preeclampsia	Proves that loss of IDO function is sufficient to drive HDP pathogenesis	(117)
Worton <i>et al</i> , 2019	Targeted therapy	Review	Kynurenine pathway	Kynurenine pathway as a novel target in treating maternal features of PE	Pharmacological intervention opportunity	(85)
Wang <i>et al</i> , 2025	Targeted therapy	<i>In vitro/in vivo</i>	Isorhynchophylline	Alleviated PE via PI3K/AKT/mTOR-mediated oxidative stress inhibition	Additional therapeutic candidate	(118)
Toghi <i>et al</i> , 2023	Targeted therapy	Gestational hypertension model	Pravastatin	Prevented MMP-2 activity and oxidative stress; enhanced NO-dependent vasodilation	Additional therapeutic candidate	(119)
Fareed <i>et al</i> , 2024	Clinical trial framework	Systematic review	Montelukast	Montelukast exposure during pregnancy not associated with increased risk of major congenital malformations , preterm birth, or low birth weight; consistent across trimesters and asthma severity	Framework in evaluating medication safety in pregnancy	(121)
Petersen <i>et al</i> , 2016	Clinical trial framework	Cohort study	Psychotropic medication	Risks and benefits of psychotropic medication in pregnancy	Framework for intervention safety evaluation	(122)
Sibiude <i>et al</i> , 2019	Clinical trial framework	Cohort study	ART	Liver enzyme elevation in pregnant women receiving ART	Importance of monitoring metabolic effects	(123)
Regan <i>et al</i> , 2025	Clinical trial framework	Cohort study	COVID-19 vaccination	Vaccination safety data around the time of conception	Safety data for future intervention trials	(124)

Vesco <i>et al</i> , 2024	Clinical trial framework	Cohort study	COVID-19 vaccination	Obstetric complications and birth outcomes after antenatal COVID-19 vaccination	Evidence base for intervention safety in pregnancy	(125)
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AhR, aryl hydrocarbon receptor; ART, antiretroviral therapy; BP, blood pressure; COVID-19, coronavirus disease 2019; HDAC, histone deacetylase; HDP, hypertensive disorders of pregnancy; IDO, indoleamine 2,3-dioxygenase; MMP-2, matrix metalloproteinase-2; NO, nitric oxide; PE, preeclampsia; RCT, randomized controlled trial; SCFA, short-chain fatty acid.
