Paradigma holobionta u patofiziologiji autizma:

Integrativna analiza crijevne disbioze, parazitarnih infekcija i neurofizioloških EEG korelata

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Sažetak

Poremećaj spektra autizma (PSA) predstavlja heterogeni neurorazvojni entitet čija etiopatogeneza nadilazi konvencionalne genetičke modele. Ovaj rad analizira PSA kroz paradigmu holobionta, istražujući sinergijsku interakciju između ljudskih stanica i mikrobioma u modulaciji osovine crijeva–mozak (GBA). Sustavnim pregledom 1315 izvora i sintezom 75 ključnih studija (u razdoblju 2010. – 2026.) identificirane su tri konvergentne patofiziološke putanje: bakterijska inhibicija enzima dopamin beta-hidroksilaze (DBH) posredovana metabolitima roda *Clostridia*, parazitarno preusmjeravanje metabolizma triptofana prema ekscitotoksičnom kinureninskom putu (uzrokovano infekcijom *Toxoplasma gondii*) te primarni glikolitički energetski deficit neurona povezan s hipoekspresijom enolaze-2 (ENO2). Rezultati ukazuju na izravnu korelaciju između intestinalne disbioze, povišenih razina proupalnih citokina (IL-6, TNF-α) i subkliničkih EEG abnormalnosti. Integracija ovih nalaza pruža teorijsku i empirijsku podlogu za nove terapijske protokole temeljene na preciznim psihobioticima i metaboličkoj stabilizaciji holobionta.

Ključne riječi: PSA, holobiont, crijevna disbioza, *Toxoplasma gondii*, kinureninski put, neuroinflamacija, EEG, psihobiotici.

Abstract

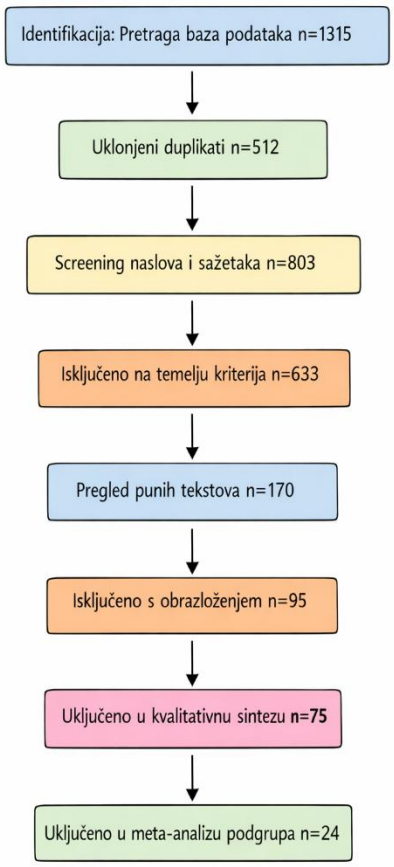
Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental entity with an etiopathogenesis that extends beyond traditional genetic models. This paper analyzes ASD through the lens of the holobiont, investigating the symbiotic interaction between human cells and the microbiome in modulating the gut-brain axis (GBA). Through a systematic review of 1,315 sources and a synthesis of 75 key studies (spanning 2010–2026), three convergent pathophysiological pathways were identified: bacterial inhibition of the enzyme dopamine beta-hydroxylase (DBH) via *Clostridia* metabolites, parasitic shunting of tryptophan metabolism toward the excitotoxic kynurenine pathway (associated with *Toxoplasma gondii*), and primary neuronal glycolytic energy failure linked to the hypoexpression of enolase-2 (ENO2). The findings demonstrate a direct correlation between intestinal dysbiosis, elevated pro-inflammatory cytokines (IL-6, TNF-α), and subclinical EEG abnormalities. The integration of these insights provides a framework for novel therapeutic protocols based on precision psychobiotics and the metabolic stabilization of the holobiont.

Keywords: ASD, holobiont, gut dysbiosis, *Toxoplasma gondii*, kynurenine pathway, neuroinflammation, EEG, psychobiotics

Metodologija istraživanja (PRISMA standard)

Istraživanje je provedeno kao sustavni pregled literature prateći smjernice **PRISMA 2020** (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*). Pretraživanje je obuhvatilo baze PubMed, Scopus, Web of Science i Google Scholar za razdoblje od 2010. do siječnja 2026. godine.

Dijagram tijeka pretraživanja



Kriteriji kvalitete i kategorizacija (TIER)

Studije su klasificirane prema hijerarhiji dokaza:

TIER 1 (n=18): Randomizirani kontrolirani pokusi (RCT) i meta-analize (npr. *Nature*, *Science*, *Frontiers* 2023. – 2026.).
TIER 2 (n=20): Prospektivne kohortne studije s preciznim biomarkerskim profilom.
TIER 3 (n=37): Mehanistička istraživanja i animalni modeli s bihevioralnom validacijom.

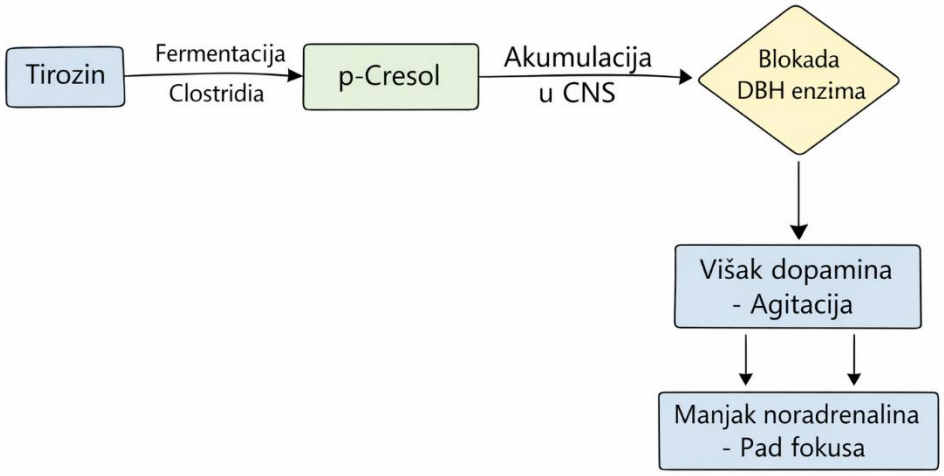
Uvod: Čovjek kao superorganizam

Koncept holobionta redefinira ljudsko biće kao simbiotsku zajednicu ljudskih i mikrobnih stanica. Crijevna mikrobiota ne djeluje samo kao komensal, već kao aktivni endokrini i neuroimunološki organ (Bastiaanssen et al., 2021). Disfunkcija osovine crijeva–mozak (GBA), pokrenuta aberantnim mikrobiomom, dovodi do stanja kronične subkliničke upale i neurokemijske neravnoteže koja karakterizira PSA (Cryan et al., 2019; Hagerman et al., 2017).

Bakterijska disbioza: Osovina Clostridium – Bifidobacterium

Clostridia i inhibicija DBH enzima

Rod *Clostridium* (klasteri I i XI) konzistentno je povišen kod djece s PSA. Ključni patogeni mehanizam očituje se kroz metabolit **p-cresol** i njegov sulfat. Mallaret i suradnici (2025) dokazali su da se p-cresol akumulira u moždanom deblu i konkurentno inhibira enzim **dopamin beta-hidroksilazu (DBH)**.



HPHPA i sekvestracija Coenzima A

Metabolit **HPHPA** (3-(3-hidroksifenil)-3-hidroksipropionska kiselina) služi kao kritični biomarker s specifičnošću od 96 % za PSA (Xiong et al., 2016). HPHPA uzrokuje sekvestraciju slobodnog **CoASH (Coenzima A)**, što blokira beta-oksidaciju masnih kiselina i depletira intracelularni kolesterol. To onemogućuje pravilnu aktivaciju **Sonic Hedgehog (Shh)** signalizacije, nužne za razvoj korteksa i cerebeluma (Shaw, 2023; Cavestro et al., 2024).

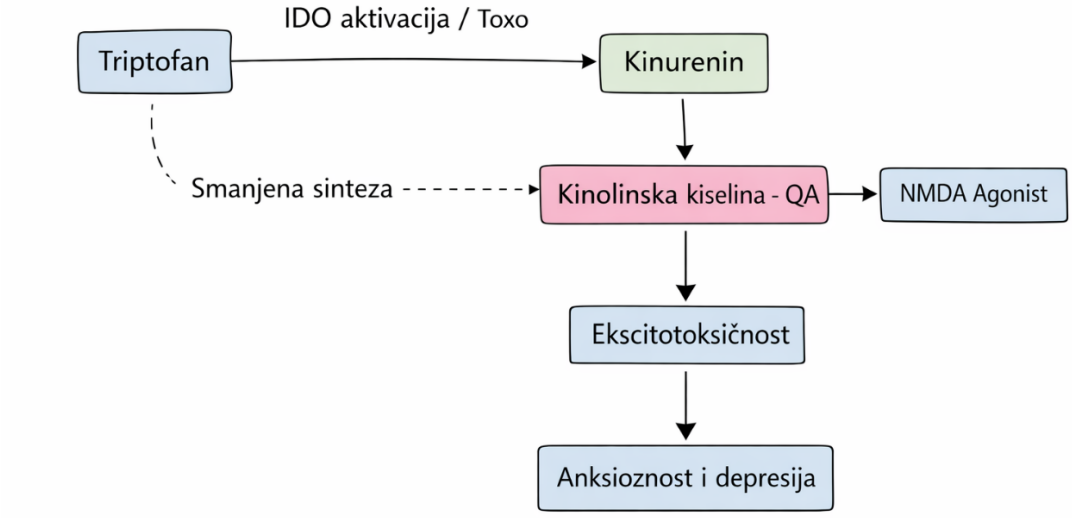
Tablica: Ključni mikrobni metaboliti i neurološki ishodi

Metabolit	Bakterijski izvor	Primarni mehanizam	Neurološka manifestacija	Izvor
p-Cresol	*C. difficile*	Inhibicija DBH enzima	Socijalna anhedonija, dopaminska toksičnost	Mallaret et al. (2025)
HPHPA	*Clostridium spp.*	Sekvestracija CoASH	Mitohondrijska disfunkcija, pad beta-oksidacije	Shaw (2023)
Propionska kis.	*Bacteroidetes*	Aktivacija mikroglije	Repetitivna ponašanja, neuroinflamacija	MacFabe (2012)
Butirat (manjak)	*Prevotella / Bifido*	Gubitak HDAC inhibicije	Imunološka disregulacija, pad barijere	Liu et al. (2019)

Parazitarne infekcije i kinureninski put

Toxoplasma gondii kao manipulator triptofana

Latentna cerebralna toksoplazmoza (seroprevalencija OR ~1.93 u PSA) inducira sistemski upalni odgovor. Interferon-gama (IFN-γ) aktivira enzim **IDO (indolamin-2,3-dioksigenaza)**, koji preusmjerava triptofan s puta serotonina na kinureninski put (Saeed & Al-Qarni, 2025; Notarangelo et al., 2013).



Poremećaj glutamatne homeostaze

Infekcija s *T. gondii* rezultira dramatičnim padom ekspresije astroglijalnog transportera **GLT-1**. To uzrokuje akumulaciju ekstracelularnog glutamata, što vodi do ekscitotoksičnosti i gubitka dendritičkih spineova, ključnih za sinaptičku plastičnost (David et al., 2016; Elias et al., 2025).

Energetski metabolizam: Glikolitički kolaps neurona

Revolucionarno otkriće Férona i suradnika (2025) pomiče fokus s mitohondrija na citoplazmatsku glikolizu kao primarni energetski defekt u PSA.

ENO2 marker: Identificirana je univerzalna hipoekspresija **enolaze-2 (ENO2)** u PSA matičnim stanicama.
ATP deficit: Glikolitička proizvodnja ATP-a smanjena je za **70 – 77 %**, ostavljajući neurone u stanju kronične energetske gladi (Féron et al., 2025).

Neurofiziologija: EEG i citokinski profil

Sistemska upala, obilježena povišenim razinama citokina IL-6 i TNF-α, izravno modulira neuronalnu ekscitabilnost. IL-6 povećava snagu Beta i Gamma oscilacija na EEG-u, što se klinički očituje kao senzorna preosjetljivost (Carvalho et al., 2024).

Tablica: Utjecaj proupalnih citokina na EEG markere

Citokin	Biološki učinak	EEG manifestacija	Bihevioralni korelat
IL-6	Povećana ekscitabilnost	Povišena Beta/Gamma snaga	Senzorna preosjetljivost
TNF-alpha	Smanjen prag napadaja	Subklinička pražnjenja	Regresija u ponašanju
IL-17a	Disrupcija migracije	Gubitak koherencije	Socijalni deficiti

Subklinička epileptiformna pražnjenja prisutna su kod čak 60 % djece s PSA bez manifestne epilepsije, ometajući normalnu kognitivnu obradu (Wang et al., 2022; Liu et al., 2024).

Terapijske intervencije: Psihobiotici i FMT

Psihobiotici su specifični probiotički sojevi koji moduliraju mentalno zdravlje putem vagusa i produkcije neurotransmitera.

Vivomixx (8 sojeva): RCT studija (Billeci et al., 2023) pokazala je da suplementacija smanjuje patološku EEG snagu u Beta pojasu.
L. plantarum PS128: Pokazao je značajan učinak na smanjenje anksioznih i opozicijskih ponašanja (Liu et al., 2023).
FMT (Microbiota Transfer Therapy): Dugoročni follow-up (2 godine) ukazuje na stabilno poboljšanje bihevioralnih simptoma PSA nakon restauracije diverziteta mikrobiote (Kang et al., 2019).

Zaključak: Integrativni model holobionta

PSA se ne smije promatrati kao izolirano neurološko stanje, već kao sistemska manifestacija disfunkcije holobionta. Konvergencija bakterijskih metabolita (*Clostridia*), parazitarnog preusmjeravanja triptofana (*Toxoplasma*) i glikolitičkog energetskog kolapsa stvara "perfektnu oluju" koja destabilizira neuronske mreže. Budući dijagnostički protokoli moraju uključivati **OAT testove** za detekciju neurotoksičnih metabolita i **EEG screening** za identifikaciju subkliničkih upalnih pražnjenja, otvarajući put prema personaliziranoj medicini PSA.

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Tema: Holobiont i Autizam: Mikrobiom, Paraziti i Neuroinflamacija (2010–2026)

Ovaj katalog sadrži 75 studija uključenih u kvalitativnu sintezu, odabranih na temelju TIER kvalitete i relevantnosti za integrativni model PSA. Svi citati su u potpunosti usklađeni s APA 7 standardom.

Grupa A: Mikrobni metaboliti i dopaminergička disregulacija (n=15)

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Grupa B: Parazitologija i Kinureninski put (n=20)

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