

## ROL DE LA MICROBIOTA INTESTINAL EN EL DESARROLLO DEL TRASTORNO DEL ESPECTRO AUTISTA.

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### RESUMEN

La microbiota humana desempeña un papel importante en diferentes procesos fisiológicos del cuerpo humano como; la protección contra agentes patógenos, el metabolismo energético, la nutrición y el desarrollo del sistema inmune entre otras. Sin embargo, el desequilibrio de algunos de estos microorganismos ha sido involucrado en el desarrollo de algunas enfermedades en el hombre como; infecciones en la piel, en las vías respiratorias altas, en el aparato genitourinario y en los intestinos. Principalmente, la disbiosis de la microbiota intestinal ha sido relacionada con enfermedades asociadas a trastornos del desarrollo mental como lo es El Trastorno Del Espectro Autista. Esta enfermedad influye directamente en la calidad de vida de los pacientes, ya que afecta el correcto funcionamiento del cerebro generando problemas cognitivos, comunicación deteriorada, comportamiento repetitivo y dificultad para la interacción social. Los diferentes problemas asociados al trastorno impactan directamente en las familias y en la economía de la salud nacional, por lo que puede ser considerado como un problema de salud pública. Debido a lo anterior es de suma importancia mostrar el rol de la microbiota intestinal en el desarrollo del Trastorno Del Espectro Autista, de tal forma que esto permita una mejor comprensión del trastorno y así influir positivamente en su prevención y tratamiento. Para poder lograr este objetivo se realizó una búsqueda bibliográfica en las bases de datos NCBI, SciELO, Redalyc, Plos one y Science Direct. Los resultados demuestran que existe una relación entre los trastornos gastrointestinales y el Trastorno Del Espectro Autista la cual es regulada por el eje Intestino-cerebro de una manera bidireccional. Finalmente se puede concluir que la disbiosis intestinal hasta el momento no es considerada una causa del desarrollo de Trastorno Del Espectro Autista, sin embargo, es un factor que regula la sintomatología de esta enfermedad mental.

**Palabras claves:** microbiota intestinal, trastorno del espectro autista, disbiosis, eje intestino-cerebro.

## ABSTRACT

The human microbiota plays an important role in different physiological processes of the human body, such as protection against pathogens, energy metabolism, nutrition and the development of the immune system, among others. However, the imbalance of some of these microorganisms has been involved in the development of some diseases in humans, such as infections in the skin, upper respiratory tract, genitourinary system and intestines. Mainly, the dysbiosis of the intestinal microbiota has been related to diseases associated with mental development disorders such as Autism Spectrum Disorder. This disease directly influences the quality of life of patients, as it affects the proper functioning of the brain generating cognitive problems, impaired communication, repetitive behavior and difficulty in social interaction. The different problems associated with the disorder directly impact families and the national health economy, so it can be considered a public health problem. Due to the above, it is very important to show the role of the intestinal microbiota in the development of the Autism Spectrum Disorder, in such a way that it allows a better understanding of the disorder and thus positively influence its prevention and treatment. In order to achieve this objective, a bibliographic search was carried out in the NCBI, SciELO, Redalyc, Plos one and Science Direct databases. The results show that there is a relationship between gastrointestinal disorders and Autism Spectrum Disorder which is regulated by the bowel-brain axis in a bidirectional manner. Finally it can be concluded that intestinal dysbiosis is not yet considered a cause of the development of Autism Spectrum Disorder, however, it is a factor that regulates the symptomatology of this mental illness.

**Keywords:** intestinal microbiota, autism spectrum disorder, dysbiosis, intestine-brain axis.

## REFERENCIAS BIBLIOGRÁFICAS

1. Bermon P, Petriz B, Kajéniené A, Prestes J, Castell L, Franco O. the microbiota: an exercise immunology perspective stéphane. *Microbiota Exerc Immunol.* 2015;(22):70–9.
2. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: the gut-brain axis. *Clin Pract.* 2017;7(4).
3. Tinahones F. La importancia de la microbiota en la obesidad. *Rev Esp Endocrinol Pediatr.* 2017;8:15–20.
4. Farías M, Silva C, Rozowski J. MICROBIOTA INTESTINAL: ROL EN OBESIDAD. *Rev Chil Nutr.* 2011;38(2):228–33.
5. Muñoz A, Diaz C, Tinahones F. Microbiota y diabetes mellitus tipo 2. *Endocrinol y Nutr.* 2016;63(10):560–8.
6. Foster J, Rinaman L, Cryan J. Stress & the gut-brain axis: Regulation by the

- microbiome. *Neurobiol Stress* [Internet]. 2017;7:124–36. Available from: <https://doi.org/10.1016/j.ynstr.2017.03.001>
7. Sherwin E, Dinan T, Cryan J. Recent developments in understanding the role of the gut microbiota in brain health and disease. *Ann N Y Acad Sci*. 2018;1420(1):5–25.
  8. Treisman G. The Microbiota in Gastrointestinal Pathophysiology The Role of the Brain–Gut–Microbiome in Mental Health and Mental Disorders [Internet]. *The Microbiota in Gastrointestinal Pathophysiology*. Elsevier Inc.; 2017. 0 p. Available from: <http://dx.doi.org/10.1016/B978-0-12-804024-9/00042-2>
  9. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, et al. Recurrence risk for autism spectrum disorders: A baby siblings research consortium study. *Pediatrics*. 2011;128(3).
  10. Aman M. Treatment planning for patients with autism spectrum disorders. *J Clin Psychiatry*. 2005;66:38–45.
  11. Risch N, Hoffmann T, Anderson M, Croen L, Grether J, Windham G. Familial recurrence of autism spectrum disorder: Evaluating genetic and environmental contributions. *Am J Psychiatry* [Internet]. 2014;171(11):1206–13. Available from: <http://ajp.psychiatryonline.org/doi/pdfplus/10.1176/appi.ajp.2014.13101359%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014905510>
  12. Pulikkan J, Manzumder A, Grace T. Role of the Gut Microbiome in Autism Spectrum Disorders. *Adv Exp Med Biol* [Internet]. 2019;1118:253–69. Available from: <http://link.springer.com/10.1007/978-3-030-05542-4>
  13. Vuong H, Hsiao E. Emerging roles for the gut microbiome in autism spectrum disorder. *Biol Psychiatry*. 2017;81(5):411–23.
  14. Fattorusso A, Di Genova L, Dell'isola GB, Mencaroni E, Esposito S. Autism spectrum disorders and the gut microbiota. *Nutrients*. 2019;11(3).
  15. Torrijo B, Gonzalez D. Influencia de la microbiota en pacientes con trastornos del comportamiento. 2017;1–34. Available from: <https://repositorio.unican.es/xmlui/bitstream/handle/10902/12432/TorrijoBuenoBeatriz.pdf?sequence=4>
  16. Kumar A, Chordia N. Role of Microbes in Human Health. *Appl Microbiol Open Access*. 2017;03(02):2–4.
  17. Collado M, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci Rep* [Internet]. 2016;6(February):1–13. Available from: <http://dx.doi.org/10.1038/srep23129>
  18. Principi N, Esposito S. Gut microbiota and central nervous system development. *J Infect* [Internet]. 2016;73(6):536–46. Available from: <http://dx.doi.org/10.1016/j.jinf.2016.09.010>
  19. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism - comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* [Internet]. 2011;11(1):22. Available from: <http://www.biomedcentral.com/1471-230X/11/22>

20. Tomova A, Husarova V, Lakatosova S, Bakos J, Vlkova B, Babinska K, et al. Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav* [Internet]. 2015;138:179–87. Available from: <http://dx.doi.org/10.1016/j.physbeh.2014.10.033>
21. Xiang Q, Loke W, Venkatanarayanan N, Lim D, Yu A, Song W. A systematic review of the role of prebiotics and probiotics in autism spectrum disorders. *Med*. 2019;55(5):1–10.
22. Madigan M, Martinko J, Parker J, Brock T, Rodríguez C, Sánchez M. *Biología de los microorganismos*. 10th, reimpr ed. Pearson Educación, editor. 2004.
23. Hug L, Baker B, Anantharaman K, Brown C, Probst A, Castelle C, et al. A new view of the tree of life. *Nat Microbiol*. 2016;1(5):1–6.
24. Tortora G, Funke B, Case C. *Introducción a la microbiología*. novena edi. Buenos Aires; 2007. 283–292, 327–330, 345–370, 389-397. p.
25. Yaeger R. Protozoa: Structure, Classification, Growth, and Development. In: Baron S, editor. *Medical Microbiology*. 4th editio. 1996.
26. Spencer L, Gómez A, Collovini E. Mecanismos de invasion del esporozoíto y merozoíto de Plasmodium. *Bionatura*. 2016;1(2):89–94.
27. Murray P, Rosenthal K, Pfaller M. *Microbiología medica*. 7 edicion. Elsevier Saunders; 2014.
28. Manoharachary C, Sridhar K, Singh R, Adholeya A, Suryanarayanan T, Rawat S, et al. Fungal biodiversity: Distribution, conservation and prospecting of fungi from India. *Curr Sci*. 2005;89(1):58–71.
29. Mukherjee D, Singh S, Kumar M, Kumar V. *Fungal Biotechnology : Role and Aspects Current Perspectives*. In: *Fungi and their Role in Sustainable Development: Current Perspectives*. 2018.
30. Beekman A, Barrow R. Fungal metabolites as pharmaceuticals. *Aust J Chem*. 2014;67(6):827–43.
31. Enyiukwu D, Ononuju C, Maranzu J. Plant Pathogenic Fungi – Novel Agents of Human Diseases: Implications for public Health. *Greener J Epidemiol Public Heal*. 2018;6(1):001–19.
32. Nosanchuk J. Review of Human Pathogenic Fungi: Molecular Biology and Pathogenic Mechanisms. *Front Microbiol*. 2015;6(February):1–2.
33. Gelderblom H. Structure and Classification of Viruses. *Med Microbiol* [Internet]. 1996;(May). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21413309>
34. Flores T, Villazante L. Clasificación de los microorganismos. *Rev Actual Clin* [Internet]. 2014;44:2309–13. Available from: [http://www.revistasbolivianas.org.bo/scielo.php?script=sci\\_arttext&pid=S2304-37682014000500002&lng=es&nrm=iso%3E](http://www.revistasbolivianas.org.bo/scielo.php?script=sci_arttext&pid=S2304-37682014000500002&lng=es&nrm=iso%3E). ISSN 2304-3768.
35. Gupta P, Rajput M, Oza T, Trivedi U, Sanghvi G. Eminence of Microbial Products in Cosmetic Industry. *Nat Products Bioprospect* [Internet]. 2019;9(4):267–78. Available from: <https://doi.org/10.1007/s13659-019-0215-0>
36. Doyle M, Steenson L, Meng J. The prokaryotes: Applied bacteriology and biotechnology. In: *The Prokaryotes: Applied Bacteriology and Biotechnology*.

2013. p. 1–393.

37. Romero C, Castañeda D, Acosta G. Determinación de la calidad bacteriológica del aire en un laboratorio de microbiología en la Universidad Distrital Francisco José de Caldas en Bogotá, Colombia. NOVA [Internet]. 2016;57(1):103–11. Available from: <http://www.scielo.org.co/pdf/nova/v14n26/v14n26a12.pdf>
38. Restrepo G, Marulanda S, Fe Y de la, Diaz A, Baldani V, Hernandez A. Bacterias solubilizadoras de fosfato y sus potencialidades de uso en la promoción del crecimiento de cultivos de importancia económica. Rev CENIC Ciencias Biológicas. 2015;46(1):63–76.
39. Castro M, Cavalett A, Spinner A, Rosa D, Jasper R, Quecine M, et al. Phylogenetic identification of marine bacteria isolated from deep-sea sediments of the eastern South Atlantic Ocean. Springerplus. 2013;2(1):1–10.
40. Ríos S, Agudelo R, Gutiérrez L. Patógenos e indicadores microbiológicos de calidad del agua para consumo humano. Rev Fac Nac Salud Pública. 2017;35(2):236–47.
41. Corrales L, Sánchez L, Quimbayo M. Microorganismos potencialmente fitopatógenos en aguas de riego proveniente de la cuenca media del río Bogotá. Nova. 2018;16(29):71–89.
42. El-Gayar K, Al Abboud M, Essa A. Characterization of thermophilic bacteria isolated from two hot springs in Jazan, Saudi Arabia. J Pure Appl Microbiol. 2017;11(2):743–52.
43. Ying Y, Meng D, Chen X, Li F. An extremely thermophilic anaerobic bacterium *Caldicellulosiruptor* sp. F32 exhibits distinctive properties in growth and xylanases during xylan hydrolysis. Enzyme Microb Technol [Internet]. 2013;53(3):194–9. Available from: <http://dx.doi.org/10.1016/j.enzmictec.2013.04.004>
44. Singh P, Singh SM, Roy U. Taxonomic characterization and the bio-potential of bacteria isolated from glacier ice cores in the High Arctic. J Basic Microbiol. 2016;56(3):275–85.
45. Mano H, Morisaki H. Endophytic Bacteria in the Rice Plant. Microbes Environ. 2008;23(2):109–17.
46. Etminani F, Harighi B. Isolation and identification of endophytic bacteria with plant growth promoting activity and biocontrol potential from wild pistachio trees. Plant Pathol J. 2018;34(3):208–17.
47. Tsuyuki Y, Kurita G, Murata Y, Takahashi T. Bacteria isolated from companion animals in Japan (2014–2016) by blood culture. J Infect Chemother [Internet]. 2018;24(7):583–7. Available from: <https://doi.org/10.1016/j.jiac.2018.01.014>
48. Reis N, Saraiva M, Duarte E, de Carvalho E, Vieira B, Evangelista N. Probiotic properties of lactic acid bacteria isolated from human milk. J Appl Microbiol. 2016;121(3):811–20.
49. Moreno M, Valladares J, Halabe J. Microbioma humano. Rev la Fac Med. 2018;61(6):7–19.
50. Kumar A, Shakya A, Mohammed G, Emerald M, Kumar V. Gut-Microbiota



- and Mental Health: Current and Future Perspectives. *J Pharmacol Clin Toxicol.* 2014;2(1):1–15.
51. Guarner F. Papel de la flora intestinal en la salud y en la enfermedad. *Nutr Hosp.* 2007;22(SUPPL. 2):14–9.
  52. Luz B, Luisa D, Martha C, Patricia DP, María Z. THE HUMAN MICROBIOTA: THE ROLE OF MICROBIAL COMMUNITIES IN HEALTH AND DISEASE. *Acta Biológica Colomb.* 2015;21(1):5–15.
  53. Grice E, Segre J. The skin microbiome. *Nat Rev Microbiol.* 2011;9(4):244–53.
  54. Rudolf R, William J. Microbiology of the skin: Resident flora, ecology, infection. *J Am Acad Dermatology* [Internet]. 1989;20(3). Available from: [http://ac.els-cdn.com.proxy-ub.rug.nl/S0190962289700487/1-s2.0-S0190962289700487-main.pdf?\\_tid=e8903b50-2f33-11e7-b39b-00000aab0f01&acdnat=1493728745\\_5cbaecb74957c0b8b7ee18c3d6a363ee](http://ac.els-cdn.com.proxy-ub.rug.nl/S0190962289700487/1-s2.0-S0190962289700487-main.pdf?_tid=e8903b50-2f33-11e7-b39b-00000aab0f01&acdnat=1493728745_5cbaecb74957c0b8b7ee18c3d6a363ee)
  55. McLaughlin J, Watterson S, Layton A, Bjourson A, Barnard E, McDowell A. Propionibacterium acnes and Acne Vulgaris: New Insights from the Integration of Population Genetic, Multi-Omic, Biochemical and Host-Microbe Studies. *Microorganisms.* 2019;7(5):128.
  56. Hernández F, Acosta J, Vázquez J, De Oca R. Identification and molecular characterization of *Corynebacterium xerosis* isolated from a sheep cutaneous abscess: First case report in Mexico. *BMC Res Notes.* 2016;9(1):11–3.
  57. Pathak R, Kasama N, Kumar R, Gautam H. *Staphylococcus epidermidis* in human skin microbiome associated with acne: A cause of disease or defence? *Res J Biotechnol.* 2013;8(12):78–82.
  58. Patiño L, Morales C. Microbiota de la piel: el ecosistema cutáneo. *Rev Colomb Dermatología y Cirugía Dermatológica* [Internet]. 2013;21(2):147–58. Available from: [www.revistasocolderma.com](http://www.revistasocolderma.com)
  59. Pato C, Melo J, Ramirez M, Friães A. *Streptococcus pyogenes* Causing Skin and soft tissue infections are enriched in the recently emerged emm89 Clade 3 and are not associated with abrogation of CovRS. *Front Microbiol.* 2018;9:1–13.
  60. Melican K, Michea Veloso P, Martin T, Bruneval P, Duménil G. Adhesion of *Neisseria meningitidis* to Dermal Vessels Leads to Local Vascular Damage and Purpura in a Humanized Mouse Model. *PLoS Pathog.* 2013;9:1–11.
  61. Schleifer K, Kloos W. Isolation and characterization of *Staphylococci* from human skin. *Int J Syst Bacteriol.* 1975;25(1):50–61.
  62. Pinto M, Hundi G, Bhat R, Bala N, Dandekeri S, Martis J, et al. Clinical and epidemiological features of coryneform skin infections at a tertiary hospital. *Indian Dermatol Online J.* 2016;7(3):168–173.
  63. Zaura E, Keijser B, Huse S, Crielaard W. Defining the healthy “core microbiome” of oral microbial communities. *BMC Microbiol.* 2009;9:1–12.
  64. Nimish P, Deshmukh R. Oral microbiome: Unveiling the fundamentals. *J Oral Maxillofac Pathol.* 2019;23(1):122–8.
  65. Netuschil N, Netuschil L. The Oral Microbiota. In: *Microbiota of the Human*

Body. 2016. p. 45–60.

66. Serrano H, Sánchez M, Cardona N. Conocimiento de la microbiota de la cavidad oral a través de la metagenómica. *CES Odontol.* 2015;28(2):112–8.
67. Wang H, Dai W, Feng X, Zhou Q, Wang H, Yang Y, et al. Microbiota Composition in Upper Respiratory Tracts of Healthy Children in Shenzhen, China, Differed with Respiratory Sites and Ages. *Biomed Res Int.* 2018;2018.
68. Morales P, Brignardello J, Gotteland M. La microbiota intestinal: Un nuevo actor en el desarrollo de la obesidad. *Rev Med Chil.* 2010;138(8):1020–7.
69. Icaza M. Microbiota intestinal en la salud y la enfermedad. *Rev Gastroenterol México* [Internet]. 2013;78(4):240–8. Available from: <http://dx.doi.org/10.1016/j.rgmx.2013.04.004>
70. Frazier T, DiBaise J, McClain C. Gut microbiota, intestinal permeability, obesity-induced inflammation, and liver injury. *J Parenter Enter Nutr.* 2011;35:14–20.
71. Rutayisire E, Huang K, Liu Y, Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol* [Internet]. 2016;1–12. Available from: <http://dx.doi.org/10.1186/s12876-016-0498-0>
72. Gómez M, Ramón J, Pérez L, Blanco J. The microbiota-gut-brain axis and its great projections. *Rev Neurol.* 2019;68(3):111–7.
73. Dieterich W, Schink M, Zopf Y. Microbiota in the Gastrointestinal Tract. *Med Sci.* 2018;6(4):116.
74. Bellmann S, Carlander D, Fasano A, Momcilovic D, Scimeca J, Waldman J, et al. Mammalian gastrointestinal tract parameters modulating the integrity, surface properties, and absorption of food-relevant nanomaterials. *Wiley Interdiscip Rev Nanomedicine Nanobiotechnology.* 2015;7(5):609–22.
75. Watari J, Chen N, Amenta P, Fukui H, Oshima T, Tomita T, et al. *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. *World J Gastroenterol.* 2014;20(18):5461–73.
76. Olveira G. Probióticos y prebióticos en la práctica clínica. *Nutr Hosp.* 2007;22(SUPPL. 2):26–34.
77. Sartor B. Microbial Influences in Inflammatory Bowel Diseases. *Gastroenterology.* 2008;134(2):577–94.
78. Otero W, Gómez M. Síndrome de intestino irritable. *Rev Cuba Med Mil.* 1997;26(1):63–8.
79. Rajilić M, Biagi E, Heilig H, Kajander K, Kekkonen R, Tims S, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology.* 2011;141(5):1792–801.
80. Kassinen A, Krogius L, Mäkivuokko H, Rinttilä T, Paulin L, Corander J, et al. The Fecal Microbiota of Irritable Bowel Syndrome Patients Differs Significantly From That of Healthy Subjects. *Gastroenterology.* 2007;133(1):24–33.
81. Spiller R. Review article: Probiotics and prebiotics in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2008;28(4):385–96.

82. Moscoso F, Quera R. Enfermedad celíaca. Revisión. *Rev Med Chil.* 2016;144:211–21.
83. Sylvia L, Odio T, Córdova ZM. Base genética de la enfermedad celiaca en el diagnóstico. *Rev Cubana Med.* 2012;51(2):170–82.
84. Girón F, Tapia S, Moriñigo M, Navas V, Serrano J, Alonso B, et al. La composición de la microbiota duodenal en niños con enfermedad celíaca activa está influenciada por el grado de enteropatía. *An Pediatr.* 2016;84(4):224–30.
85. Sjöberg V, Sandström O, Hedberg M, Hammarström S, Hernell O, Hammarström M. Intestinal T-cell Responses in Celiac Disease - Impact of Celiac Disease Associated Bacteria. *PLoS One.* 2013;8(1).
86. Guo Q, Wang Y, Xu D, Nossent J, Pavlos N, Xu J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. *Bone Res* [Internet]. 2018;6(1). Available from: <http://dx.doi.org/10.1038/s41413-018-0016-9>
87. Firestein G. Evolving concepts of rheumatoid arthritis. *Nature.* 2003;423(6937):356–61.
88. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med* [Internet]. 2015;21(8):895–905. Available from: <http://dx.doi.org/10.1038/nm.3914>
89. Omran Y Al, Aziz Q. The Brain-Gut Axis in Health and Disease. In: *Microbial Endocrinology: The Microbiota-Gut-Brain Axis in Health and Disease* [Internet]. Springer; 2014. p. 135–53. Available from: [https://link.springer.com/chapter/10.1007%2F978-1-4939-0897-4\\_6](https://link.springer.com/chapter/10.1007%2F978-1-4939-0897-4_6)
90. Zhao L, Xiong Q, Sary C, Mahgoub O, Ye Y, Gu L, et al. Bidirectional gut-brain-microbiota axis as a potential link between inflammatory bowel disease and ischemic stroke. *J Neuroinflammation.* 2018;15(1):1–11.
91. Sudo N. Role of gut microbiota in brain function and stress-related pathology. *Biosci Microbiota, Food Heal.* 2019;38(3):75–80.
92. Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. *Sci China Life Sci.* 2016;59(10):1006–23.
93. Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J Neurogastroenterol Motil.* 2019;25(1):40–60.
94. Valles M, Falony G, Darzi Y, Tigchelaar E, Wang J, Tito R, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol* [Internet]. 2019;4(4):623–32. Available from: <http://dx.doi.org/10.1038/s41564-018-0337-x>
95. Yang B, Wei J, Ju P, Chen J. Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review. *Gen Psychiatry.* 2019;32(2):1–9.
96. Critchfield JW, Van Hemert S, Ash M, Mulder L, Ashwood P. The potential role of probiotics in the management of childhood autism spectrum disorders. *Gastroenterol Res Pract.* 2011;2011.
97. I G, C H. *Handbook of Depression.* New York: The Guilford Press; 2009.
98. Grober G. Major depressive disorder. *J Psychiatry.* 2013;19:157–63.
99. Cheung S, Goldenthal A, Uhlemann A, Mann J, Miller J, Sublette E.



- Systematic review of gut microbiota and major depression. *Front Psychiatry*. 2019;10(34):1–17.
100. Steenbergen L, Sellaro R, Hemert S Van, Bosch J, Colzato L. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behav Immun*. 2015;48:258–64.
  101. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin Neurosci*. 2015;17(3):327–35.
  102. Martínez M, López D. Trastornos de ansiedad. *Rev Neurol Neurocir y Psiquiatr* [Internet]. 2011;44(3):101–7. Available from: <https://www.medigraphic.com/pdfs/revneuneupsi/nnp-2011/nnp113d.pdf><http://www.medigraphic.com/pdfs/revneuneupsi/nnp-2011/nnp113d.pdf>
  103. Korolev I. Alzheimer's Disease: A Clinical and Basic Science Review. *Med Student Res J*. 2014;4:24–33.
  104. Donoso A. La enfermedad de Alzheimer. *Rev Chil Neuropsiquiatr*. 2003;41(2):13–22.
  105. Vogt N, Kerby R, Dill-McFarland K, Harding S, Merluzzi A, Johnson S, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep* [Internet]. 2017;7(1):1–11. Available from: <http://dx.doi.org/10.1038/s41598-017-13601-y>
  106. Naranjo M. Una revisión teórica sobre el estrés y algunos aspectos relevantes de este en el ámbito educativo. *Rev Educ*. 2009;33(2):171–90.
  107. Herrera D, Coria G, Muñoz D, Graillet O, Aranda G, Rojas F, et al. Impacto del estrés psicosocial en la salud. *Neurobiología*. 2017;8(17):1–23.
  108. Karl P, Hatch A, Arcidiacono S, Pearce S, Pantoja I, Doherty L, et al. Effects of psychological, environmental and physical stressors on the gut microbiota. *Front Microbiol*. 2018;9:1–32.
  109. Molina G, Rodriguez M, Roman P, Sanchez N, Cardona D. Stress and the gut microbiota-brain axis. *Behav Pharmacol* [Internet]. 2019;187–200. Available from: <https://insights.ovid.com/pubmed?pmid=30844962>
  110. Zijlmans M, Korpela K, Riksen M, de Vos W, de Weerth C. Maternal prenatal stress is associated with the infant intestinal microbiota. *Psychoneuroendocrinology* [Internet]. 2015;53:233–45. Available from: <http://dx.doi.org/10.1016/j.psyneuen.2015.01.006>
  111. Carrascón C. Señales de alerta de los trastornos del espectroautista. *Actual Pediatr* [Internet]. 2016;3:95–8. Available from: [https://www.aepap.org/sites/default/files/2em.2\\_senales\\_de\\_alerta\\_de\\_los\\_trastornos\\_del\\_espectro\\_autista.pdf](https://www.aepap.org/sites/default/files/2em.2_senales_de_alerta_de_los_trastornos_del_espectro_autista.pdf)
  112. Mannion A, Leader G, Healy O. An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with Autism Spectrum Disorder. *Res Autism Spectr Disord*. 2013;7(1):35–42.
  113. Bonilla M, Chaskel R. Trastorno del espectro autista. *Trastor del espectro autista*. 2016;15(1):19–29.
  114. Heberling C, Dhurjati P, Sasser M. Hypothesis for a systems connectivity model of autism spectrum disorder pathogenesis: Links to gut bacteria ,

- oxidative stress , and intestinal permeability. *Med Hypotheses* [Internet]. 2013;80(3):264–70. <http://dx.doi.org/10.1016/j.mehy.2012.11.044>
115. Finegold S, Molitoris D, Song Y, Liu C, Vaisanen M, Bolte E, et al. Gastrointestinal Microflora Studies in Late-Onset Autism. *Clin Infect Dis*. 2002;35(s1):S6–16.
  116. Finegold S, Dowd S, Gontcharova V, Liu C, Henley K, Wolcott R, et al. Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe* [Internet]. 2010;16(4):444–53. Available from: <http://dx.doi.org/10.1016/j.anaerobe.2010.06.008>
  117. Kang D, Park J, Ilhan Z, Wallstrom G, LaBaer J, Adams J, et al. Reduced Incidence of *Prevotella* and Other Fermenters in Intestinal Microflora of Autistic Children. *PLoS One*. 2013;8(7).
  118. de Angelis M, Francavilla R, Piccolo M, De Giacomo A, Gobbetti M. Autism spectrum disorders and intestinal microbiota. *Gut Microbes*. 2015;6(3):207–13.
  119. Pulikkan J, Maji A, Dhakan DB, Saxena R, Mohan B, Anto MM, et al. Gut Microbial Dysbiosis in Indian Children with Autism Spectrum Disorders. *Microb Ecol*. 2018;76(4):1102–14.
  120. Molloy C, Manning P. Prevalence of chronic gastrointestinal symptoms in children with autism and. *Seage Journals*. 2003;7(2):165–71.
  121. Ming X, Brimacombe M, Chaaban J, Zimmerman B, Wagner G. Autism Spectrum Disorders: Concurrent Clinical Disorders. *J Child Neurol*. 2008;23(1):6–13.
  122. Nikolov R, Bearss K, Lettinga J, Erickson C, Rodowski M, Aman M, et al. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *J Autism Dev Disord*. 2009;39(3):405–13.
  123. Li Q, Zhou JM. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. *Neuroscience*. 2016;324:131–9.
  124. Finegold S. *Desulfovibrio* species are potentially important in regressive autism. *Med Hypotheses* [Internet]. 2011;77(2):270–4. Available from: <http://dx.doi.org/10.1016/j.mehy.2011.04.032>
  125. MacFabe D. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. *Microb Ecol Health Dis*. 2012;23(1):1–24.
  126. Argou I, Zeidán F. *Clostridium* Bacteria and Autism Spectrum Conditions: A Systematic Review and Hypothetical Contribution of Environmental Glyphosate Levels. *Med Sci*. 2018;6(2):1–11.
  127. Al-Lahham S, Peppelenbosch M, Roelofsen H, Vonk R, Venema K. Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms. *Biochim Biophys Acta - Mol Cell Biol Lipids* [Internet]. 2010;1801(11):1175–83. Available from: <http://dx.doi.org/10.1016/j.bbalip.2010.07.007>
  128. DeCastro M, Nankova B, Shah P, Patel P, Mally P, Mishra R, et al. Short chain fatty acids regulate tyrosine hydroxylase gene expression through a cAMP-dependent signaling pathway. *Mol Brain Res*. 2005;142(1):28–38.
  129. MacFabe D, Cain N, Boon F, Ossenkopp K, Cain D. Effects of the enteric

- bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: Relevance to autism spectrum disorder. *Behav Brain Res* [Internet]. 2011;217(1):47–54. Available from: <http://dx.doi.org/10.1016/j.bbr.2010.10.005>
130. Hong J, Jia Y, Pan S, Jia L, Li H, Han Z. Butyrate alleviates high fat diet-induced obesity through activation of adiponectin-mediated pathway and stimulation of mitochondrial function in the skeletal muscle of mice. *Oncotarget*. 2016;7(35):56071–82.
131. Takuma K, Hara Y, Kataoka S, Kawanai T, Maeda Y, Watanabe R, et al. Chronic treatment with valproic acid or sodium butyrate attenuates novel object recognition deficits and hippocampal dendritic spine loss in a mouse model of autism. *Pharmacol Biochem Behav* [Internet]. 2014;126:43–9. Available from: <http://dx.doi.org/10.1016/j.pbb.2014.08.013>