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Resveratrol as a modulator of the gut-brain axis in irritable bowel syndrome

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Abstract

Resveratrol, a polyphenolic compound synthesized by plants, has garnered increasing attention in recent years for its potential pharmacological applications. Notably, it has been explored as a modulator of the gut-brain axis, particularly concerning irritable bowel syndrome (IBS). IBS is a life-quality impairing condition characterized by recurrent abdominal pain associated with defecation, as well as alterations in stool frequency or form. This review provides a comprehensive overview of the role of the gut-brain axis in IBS, with a specific focus on the potential of resveratrol as a modulator of this axis and its therapeutic implications for IBS management.

Running title: Resveratrol in irritable bowel syndrome

Keywords: resveratrol, irritable bowel syndrome, gut-brain axis

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Introduction

Resveratrol is a polyphenolic compound naturally synthesized by various plants, such as grapevines, in response to environmental stressors [1]. In recent years, there has been growing interest in this compound due to its potential pharmacological applications, including its use in IBS [2,3].

According to the Rome IV criteria, which are diagnostic guidelines used to classify functional gastrointestinal disorders, IBS is characterized by recurrent abdominal pain occurring at least one day per week over a three-month period, associated with at least two of the following: defecation, a change in stool frequency, or a change in stool form. The global prevalence of IBS, based on these criteria, is estimated to be approximately 3.6%-4.0% [4]. There is evidence that patients with this condition have a significantly impaired quality of life [5]. Because of its impact on patients' well-being and healthcare systems, it is a noteworthy problem.

Therapeutic approaches for IBS often involve dietary modifications and symptomatic management as the first-line treatment. Gut-brain axis modulators, including antidepressants, are typically recommended as second-line options [6]. Recent studies have highlighted the potential role of resveratrol as a modulator of the gut-brain axis, which underlies the pathophysiology of IBS [2,3]. As a result, resveratrol has the potential to be applied in the treatment of this disorder.

Therefore, this article aims to review the theoretical basis and potential clinical use of resveratrol in IBS.

Gut-brain axis in IBS

The pathophysiology of IBS remains complex and multifactorial, with many aspects still not fully clarified. However, substantial evidence suggests that dysfunction of the gut-brain axis is one of the key factors. The gut-brain axis is defined as the bidirectional communication network between the gastrointestinal tract and the central nervous system (CNS), mediated through neural, endocrine and immune systems. Much research indicates that the microbiome should be included in this axis as it impacts both immune and endocrine responses.

The brain-gut axis comprises several key components, including the enteric nervous system (ENS), which consists of two primary plexuses: the myenteric plexus, responsible for regulating the motility of intestinal smooth muscle, and the submucosal plexus, which modulates mucosal sensation, secretion, and absorption. Additionally, the CNS and the autonomic nervous system (ANS) influence gastrointestinal motility, secretion, and blood flow. The hypothalamic-pituitary-adrenal (HPA) axis also plays a role in gastrointestinal function by responding to physical and psychological stimuli [7-9]. Disruptions in advanced brain networks may influence cognitive and emotional functions, potentially leading to impaired pain management and increased levels of anxiety and depression, which are commonly observed in chronic pain disorders and IBS [8,10].

Mechanisms of serotonin signaling in the gut-brain axis

The crucial molecule in the gut-brain axis is serotonin (5-HT) as it affects peristalsis, nociception, visceral inflammation, immune response, and brain activity, all of which take part in the pathology of IBS [11]. The vast majority (~90%) of 5-HT is produced by enterochromaffin cells in the gut [12] and approximately 5-10% is produced by serotonergic neurons which most originate from the raphe nuclei in the brain stem [13].

Serotonin exerts its effects through 5-HT receptors, which are categorized into seven groups based on their structural characteristics, signal transduction mechanisms, and pharmacological profiles. The 5-HT receptors are primarily G protein-coupled receptors (GPCRs), with the exception of the 5-HT3 receptor, which functions as a ligand-gated ion channel.

The 5-HT3 receptors are located in the ENS and modulate signaling via afferent fibers from the gastrointestinal tract. This signaling subsequently affects the brain's stress circuitry, involving the paraventricular nucleus, hippocampus, amygdala, locus coeruleus, raphe nuclei, and the HPA axis. These interactions may contribute to the development of hyperalgesia and allodynia, which are characteristic of IBS [14].

5-HT4 receptors are localized on enteric neurons and smooth muscle cells. Upon activation, these receptors facilitate the release of acetylcholine from enteric interneurons and motor neurons, thereby enhancing and sustaining propulsive gastrointestinal motility [14].

5-HT7 is predominantly expressed in the vascular and extravascular smooth muscles of the gastrointestinal (GI) tract, including the stomach, small intestine, and colon. They act through intrinsic primary afferent neurons (IPANs), where receptor activation produces slow excitatory postsynaptic potentials, leading to muscle relaxation. Overstimulation of 5-HT7 receptors may contribute to abdominal bloating and exaggerated muscle relaxation, associated with functional bowel disorders [14,15].

Resveratrol as modulator of gut-brain axis

The researchers have highlighted resveratrol as a regulator in multiple organs such as the pancreas, liver, brain, and gut, and it regulates the gut-brain axis [16-18]. It is especially pivotal in regulating glucose and hepatic lipid homeostasis through Sirtuin (SIRT)-1 activation [17,19]. SIRT-1 is an NAD+-dependent deacetylase that modifies gene expression through histone deacetylation. Resveratrol

is thought to regulate the Glucagon-like peptide-1 (GLP-1) and 5-HT pathways. Both are proven to be essential hormones for the gut-brain axis [20,21].

GLP-1 is a peptide made up of amino acids, which comes from the preproglucagon gene expressed in pancreatic alpha cells, intestinal L-cells, and certain neurons in the brainstem and hypothalamus. GLP-1's effects are produced through the GLP-1 receptors, found in pancreatic β-cells, as well as in other tissues such as neurons in specific brain regions, the peripheral afferent parasympathetic nervous system, atrial cardiac myocytes, pulmonary endothelial cells, kidney, and the GI tract [21,22].

Dao et al. found that in a high-fat-fed diabetes mouse model, resveratrol increases the release of GLP-1 [23]. Pegah et al. discovered that the combination of resveratrol and probiotics significantly increased GLP-1 and total antioxidant capacity in non-diabetic rats compared to the diabetic group [24]. However, a study conducted by Knop et al. demonstrated that resveratrol does not directly affect the release of GLP-1 [25]. Resveratrol may enhance the effect of GLP-1 in the gut and CNS by activating various genes such as SIRT1 and Foxo genes [16]. The FOXO family of proteins are transcription factors involved in various physiological and pathological processes, such as cellular homeostasis, stem cell maintenance, cancer, metabolic, and cardiovascular diseases [26]. Therefore, the mechanism of resveratrol on the release of GLP-1 remains controversial to date.

Another important pathway that has been proven to participate in regulating gastrointestinal motility involves the release and storage of nearly 90% of a hormone by enteroendocrine cells in the gastrointestinal tract, specifically the 5-HT [27]. In a study conducted by Yanez et al., it was shown that resveratrol inhibited the uptake of 5-HT by the isolated synaptic terminals called synaptosomes in the rat brain [28]. Another study by Xu et al. also demonstrated antidepressant-like activity in a chronic stress model in rodents through selective inhibition of Monoamine Oxidase A compared with Monoamine Oxidase B (which are responsible for oxidizing serotonin, norepinephrine, epinephrine phenylethylamine, and benzylamine), maintaining 5-HT and noradrenaline levels [29]. The evidence suggests that the mechanism through which resveratrol may control 5-HT and its receptor, as well as modulate the release of 5-HT, is by regulating GLP-1 [30].

One more way resveratrol can improve the gut-brain axis is by interacting with gut microbiota. Mar Larrosa et al., discovered that resveratrol can improve the gut health of rats with colitis. They found that resveratrol increases beneficial bacteria such as lactobacilli and bifidobacteria while inhibiting harmful enterobacteria. This, in turn, leads to improving the architecture of colonic mucosa and reduced levels of colonic mucosa prostaglandin E2 (PGE-2), cyclooxygenase-2 (Cox-2), PGE synthase, nitric oxide (NO), and systemic inflammation markers. These findings suggest that resveratrol has gut health benefits and exhibits antioxidative and anti-inflammatory effects. In a study conducted by Chen et al., it was found that resveratrol changes the microbiota by inhibiting the growth of Escherichia and Actinobacillus while promoting the proliferation of Bacteroides, Lactobacillus, and Bifidobacterium in piglets [31]. Additionally, Diaz-Gerevini et al. suggested that resveratrol modulates the gut microbiota by activating anti-inflammaStory lipid mediators, such as lipoxin A4, resolvins, protectins, and maresins [32].

Resveratrol in IBS

The studies revealed that resveratrol has antioxidant and anti-inflammatory effects [3,33]. Roudsari et al. summarized the potential mechanisms through which resveratrol affects various pathways. These mechanisms include the regulation of phosphodiesterase-4 (PDE4), mitogen-activated protein kinases (MAPK), Cyclooxygenase-1 and -2 (COX-1, COX-2), Myeloid differentiation primary response 88 (MyD88), and Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). These actions lead to decreased levels of IL-8 (Interleukin-8), PGE2 (Prostaglandin E2), IL-1β (Interleukin-1beta), IL-6 (Interleukin-6), iNOS (Inducible nitric oxide synthase), TNF-α (Tumor necrosis factor alpha), and IFNγ (Interferon-gamma), possibly alleviating the symptoms of IBS [33]. Resveratrol also provides neuroprotection by balancing Treg/Th17 and Th1/Th2 ratios in the small intestine, reducing pro-inflammatory cytokines and intestinal vascular permeability [34]. A study conducted on porcine intestinal enterocytes demonstrates that resveratrol can directly protect these cells against oxidative stress through the PI3K/Akt-mediated Nrf2 signaling pathway (nuclear factor erythroid 2-related factor (Nrf2) signaling pathway is activated by the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)) [35]. Another study demonstrated that treatment with resveratrol significantly improved both central nervous and peripheral symptoms in IBS-like animal models by differentially regulating 5-HT levels in the brain and the intestine [2].

Pharmacokinetic analyses indicate that resveratrol can be detected in both plasma and the brain. It leads to both peripheral impacts, such as anti-inflammatory and antioxidant effects, and central effects, such as neuroprotection. [36, 37]. It has been established that nutraceuticals rich in biophenols may serve as an effective and safe adjuvant treatment for managing Inflammatory Bowel Disease and IBS. There is stronger evidence supporting the use of resveratrol for treating Crohn's disease and ulcerative colitis [38].

Conclusions

IBS pathophysiology is complex and not yet fully understood, with the gut-brain axis dysfunction playing a crucial role in its development. Resveratrol as a modulator of the gut-brain axis has the potential to be beneficial for patients with this disorder, as shown in animal models. However, the lack of clinical studies leaves much unknown about its effectiveness in humans. Consequently, further research in this area is needed.

Ethical approval

This conducted study is not related to either human or animal use.

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Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Teka T, Zhang L, Ge X, Li Y, Han L, Yan X. Stilbenes: source plants, chemistry, biosynthesis, pharmacology, application and problems related to their clinical application – a comprehensive review. Phytochemistry. 2022;197:113128; DOI:10.1016/J.PHYTOCHEM.2022.113128.
2. Yu YC, Li J, Zhang M, Pan JC, Yu Y, Zhang JB, Zheng L, Si JM, Xu Y. Resveratrol improves brain-gut axis by regulation of 5-HT-dependent signaling in the rat model of irritable bowel syndrome. Front Cell Neurosci. 2019;13:30; DOI:10.3389/FNCEL.2019.00030.
3. Xu Y, Cui SY, Ma Q, Shi J, Yu Y, Li JX, Zheng L, Zhang Y, Si JM, Yu YC. Trans-resveratrol ameliorates stress-induced irritable bowel syndrome-like behaviors by regulation of brain-gut axis. Front Pharmacol. 2018;9:631; DOI:10.3389/FPHAR.2018.00631.
4. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, Whitehead WE, Dumitrascu DL, Fang X, Fukudo S, Kellow J, Okeke E, Quigley EMM, Schmulson M, Whorwell P, Archampong T, Adibi P, Andresen V, Benninga MA, Bonaz B, Bor S, Fernandez LB, Choi SC, Corazziari ES, Francisconi C, Hani A, Lazebnik L, Lee YY, Mulak A, Rahman MM, Santos J, Setshedi M, Syam AF, Vanner S, Wong RK, Lopez-Colombo A, Costa V, Dickman R, Kanazawa M, Keshteli AH, Khatun R, Maleki I, Poitras P, Pratap N, Stefanyuk O, Thomson S, Zeevenhooven J, Palsson OS. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology. 2021;160(1):99-114.e3; DOI:10.1053/J.GASTRO.2020.04.014.
5. Kopczynska M, Mokros L, Pietras T, Malecka-Panas E. Quality of life and depression in patients with irritable bowel syndrome. Prz Gastroenterol. 2018;13(2):102-8; DOI:10.5114/PG.2018.75819.
6. Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, Agrawal A, Aziz I, Farmer AD, Eugenicos MP, Moss-Morris R, Yiannakou Y, Ford AC. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021;70(7):1214-40; DOI:10.1136/GUTJNL-2021-324598.
7. Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, O'Mahony S, Shanahan F, Keeling PW. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology. 2006;130(2):304-11; DOI:10.1053/J.GASTRO.2005.11.033.
8. Fichna J, Storr MA. Brain-gut interactions in IBS. Front Pharmacol. 2012;3:127; DOI:10.3389/FPHAR.2012.00127.
9. Shaikh SD, Sun N, Canakis A, Park WY, Weber HC. Irritable bowel syndrome and the gut microbiome: a comprehensive review. J Clin Med. 2023;12(7):2558; DOI:10.3390/JCM12072558.
10. Piché M, Bouin M, Arsenault M, Poitras P, Rainville P. Decreased pain inhibition in irritable bowel syndrome depends on altered descending modulation and higher-order brain processes. Neuroscience. 2011;195:166-75; DOI:10.1016/J.NEUROSCIENCE.2011.08.040.
11. Yuan Y, Wang X, Huang S, Wang H, Shen G. Low-level inflammation, immunity, and brain-gut axis in IBS: unraveling the complex relationships. Gut Microbes. 2023;15(2): 2263209; DOI:10.1080/19490976.2023.2263209.
12. Layunta E, Buey B, Mesonero JE, Latorre E. Crosstalk between intestinal serotonergic system and pattern recognition receptors on the microbiota–gut–brain axis. Front Endocrinol (Lausanne). 2021;12:748254; DOI:10.3389/FENDO.2021.748254.
13. Hornung JP. The human raphe nuclei and the serotonergic system. J Chem Neuroanat. 2003;26(4):331-43; DOI:10.1016/j.jchemneu.2003.10.002.
14. Stasi C, Bellini M, Bassotti G, Blandizzi C, Milani S. Serotonin receptors and their role in the pathophysiology and therapy of irritable bowel syndrome. Tech Coloproctol. 2014;18(7):613-21; DOI:10.1007/S10151-013-1106-8.
15. Guzel T, Mirowska-Guzel D. The role of serotonin neurotransmission in gastrointestinal tract and pharmacotherapy. Molecules. 2022;27(5):1680; DOI:10.3390/MOLECULES27051680.
16. Chung JY, Jeong JH, Song J. Resveratrol modulates the gut-brain axis: focus on glucagon-like peptide-1, 5-HT, and gut microbiota. Front Aging Neurosci. 2020;12:588044; DOI:10.3389/FNAGI.2020.588044.
17. Caron AZ, He X, Mottawea W, Seifert EL, Jardine K, Dewar-Darch D, Cron GO, Harper ME, Stintzi A, McBurney MW. The SIRT1 deacetylase protects mice against the symptoms of metabolic syndrome. FASEB J. 2014;28(3):1306-16; DOI:10.1096/FJ.13-243568.
18. Kumar A, Negi G, Sharma SS. Neuroprotection by resveratrol in diabetic neuropathy: concepts & mechanisms. Curr Med Chem. 2013;20(36):4640-5; DOI:10.2174/09298673113209990151.
19. Baur JA. Resveratrol, sirtuins, and the promise of a DR mimetic. Mech Ageing Dev. 2010;131(4):261-9; DOI:10.1016/J.MAD.2010.02.007.
20. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology. 2007;132(1):397-414; DOI:10.1053/J.GASTRO.2006.11.002
21. Salehi M, Purnell JQ. The role of glucagon-like peptide-1 in energy homeostasis. Metab Syndr Relat Disord. 2019;17(4):183-91; DOI:10.1089/MET.2018.0088.
22. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131-57; DOI:10.1053/J.GASTRO.2007.03.054.
23. Dao TM, Waget A, Klopp P, Serino M, Vachoux C, Pechere L, Drucker DJ, Champion S, Barthélemy S, Barra Y, Burcelin R, Sérée E. Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. PLoS One. 2011;6(6): e20700; DOI:10.1371/JOURNAL.PONE.0020700.
24. Pegah A, Abbasi-Oshaghi E, Khodadadi I, Mirzaei F, Tayebinai H. Probiotic and resveratrol normalize GLP-1 levels and oxidative stress in the intestine of diabetic rats. Metabol Open. 2021;10:100093; DOI:10.1016/J.METOP.2021.100093.
25. Knop FK, Konings E, Timmers S, Schrauwen P, Holst JJ, Blaak EE. Thirty days of resveratrol supplementation does not affect postprandial incretin hormone responses, but suppresses postprandial glucagon in obese subjects. Diabet Med. 2013;30(10):1214-8; DOI:10.1111/DME.12231.
26. Santos BF, Grenho I, Martel PJ, Ferreira BI, Link W. FOXO family isoforms. Cell Death Dis. 2023;14(12):797; DOI:10.1038/s41419-023-06177-1.
27. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, Niesler B, Quigley EM, Rajilić-Stojanović M, Schemann M, Schwille-Kiuntke J, Simren M, Zipfel S, Spiller RC. Irritable bowel syndrome. Nat Rev Dis Primers. 2016;2:16014; DOI:10.1038/NRDP.2016.14.
28. Yáñez M, Fraiz N, Cano E, Orallo F. Inhibitory effects of cis- and trans-resveratrol on noradrenaline and 5-hydroxytryptamine uptake and on monoamine oxidase activity. Biochem Biophys Res Commun. 2006;344(2):688-95; DOI:10.1016/J.BBRC.2006.03.190.
29. Xu Y, Wang Z, You W, Zhang X, Li S, Barish PA, Vernon MM, Du X, Li G, Pan J, Ogle WO. Antidepressant-like effect of trans-resveratrol: involvement of serotonin and noradrenaline system. Eur Neuropsychopharmacol. 2010;20(6):405-13; DOI:10.1016/J.EURONEURO.2010.02.013.
30. Lund ML, Egerod KL, Engelstoft MS, Dmytriyeva O, Theodorsson E, Patel BA, Schwartz TW. Enterochromaffin 5-HT cells – A major target for GLP-1 and gut microbial metabolites. Mol Metab. 2018;11:70-83; DOI:10.1016/J.MOLMET.2018.03.004.
31. Chen Y, Zhang H, Chen Y, Jia P, Ji S, Zhang Y, Wang T. Resveratrol and its derivative pterostilbene ameliorate intestine injury in intrauterine growth-retarded weanling piglets by modulating redox status and gut microbiota. J Animal Sci Biotechnol. 2021;12(1):70; DOI:10.1186/S40104-021-00589-9.
32. Diaz-Gerevini GT, Repossi G, Dain A, Tarres MC, Das UN, Eynard AR. Beneficial action of resveratrol: How and why? Nutrition. 2016;32(2):174-8; DOI:10.1016/J.NUT.2015.08.017.
33. Roudsari NM, Lashgari N, Momtaz S, Farzaei MH, Marques AM, Abdolghaffari AH. Natural polyphenols for the prevention of irritable

bowel syndrome: molecular mechanisms and targets; a comprehensive review. DARU J Pharm Sci. 2019;27(2):755-80; DOI:10.1007/S40199-019-00284-1.
34. Dou Z, Rong X, Zhao E, Zhang L, Lv Y. Neuroprotection of resveratrol against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting gut-brain axis. Cell Mol Neurobiol. 2019;39(6):883-98; DOI:10.1007/S10571-019-00687-3.
35. Zhuang Y, Wu H, Wang X, He J, He S, Yin Y. Resveratrol attenuates oxidative stress-induced intestinal barrier injury through PI3K/Akt-mediated Nrf2 signaling pathway. Oxid Med Cell Longev. 2019;2019:7591840; DOI:10.1155/2019/7591840.
36. Sale S, Verschoyle RD, Boocock D, Jones DJL, Wilsher N, Ruparelia KC, Potter GA, Farmer PB, Steward WP, Gescher AJ. Pharmacokinetics in mice and growth-inhibitory properties of the putative cancer chemopreventive agent resveratrol and the synthetic analogue trans 3,4,5,4′-tetramethoxystilbene. Br J Cancer. 2004;90(3):736-44; DOI:10.1038/SJ.BJC.6601568.
37. Frozza RL, Bernardi A, Paese K, Hoppe JB, Silva Td, Battastini AMO, Pohlmann AR, Guterres SS, Salbego C. Characterization of trans-resveratrol-loaded lipid-core nanocapsules and tissue distribution studies in rats. J Biomed Nanotechnol. 2010;6(6):694-703; DOI:10.1166/JBN.2010.1161.
38. Giang J, Lan X, Crichton M, Marx W, Marshall S. Efficacy and safety of biophenol-rich nutraceuticals in adults with inflammatory gastrointestinal diseases or irritable bowel syndrome: a systematic literature review and meta-analysis. Nutr Diet. 2021;79(1):76-93; DOI:10.1111/1747-0080.12672.