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Oral Phyto-thymol ameliorates the stress induced IBS symptoms

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Physical stressors play a crucial role in the progression of irritable bowel syndrome (IBS). Here we report a heterogeneous physical stress induced IBS rat model which shows depression and subsequent modulation of IBS by oral treatment of thymol. Oral administration of Thymol reduces the stress induced IBS significantly altering the stress induced gastrointestinal hypermotility, prolonged the whole gut transit time, and increased abdominal withdrawal reflex suggesting gastrointestinal hypermotility and visceral discomfort caused the onset of depression. Immunohistochemical analysis in small intestine and colon of rats shows the decreased 5-HT_{3A}R expression level while thymol treatment normalized the 5-HT_{3A}R expression in the stressed rats. Molecular docking studies showed that thymol competes with endogenous serotonin and an antagonist, Tropicsetron and all have similar binding energies to 5-HT_{3A}R. Molecular dynamics simulations revealed that thymol and tropisetron might have similar effects on 5-HT_{3A}R. Our study suggest that thymol improves IBS symptoms through 5-HT_{3A}R, could be useful for the treatment of IBS.

Stress remains an inextricable part of our life throughout the history of civilization, and perhaps changed its course during the modern era in terms of urbanization and lifestyle. Causes and circumstances of stress could vary in different instances, subsequently changing the manifestations of the cause–effect relationship. Stress in life comes from various origins, such as physical trauma, early life events, loss of parents, physical/sexual abuse, and acts as predisposing risk factors for the development of irritable bowel syndrome (IBS), a functional gastrointestinal disorder (FGID). Physical stressors can alter the gut brain axis affecting the visceral events¹. Traumatic events can induce changes in the brain sensory response that modulates the neuroendocrine hypothalamus–pituitary–adrenal (HPA) crosstalk^{1–4}. A “fight” response generated due to threat (stressor) activates a feedback mechanism to quench the stress to reinstate the system allostasis^{2,5}. However a prolonged stressor can ruin the adaptive system to achieve stress homeostasis, and could subsequently turn into pathogenesis of whole body disorders including gastrointestinal tract (GI) of viscera^{6,7}. The consequence of stress episodes and associated anxiety is often compensated in adults at the cost of irritable bowel syndrome (IBS)⁴. Hence social stress and relevant maladaptation of life style are often buffered at the expense of IBS. IBS is a complex, polygenic disorder that often includes various symptoms such as abdominal pain and discomfort, visceral hyperalgesia, altered fecal output and GI transit time⁸. Visceral pain can arise from wide arrays of disorders such as gallstone, pancreatitis, esophageal reflux and many others⁹. Nociceptive pain stems from the central nervous system (CNS) innervating viscera to the site of signal transmission¹⁰. The outcome of visceral pain management has remained unsatisfactory during the last decades including a cost burden of diminished quality of life. However, efforts are ongoing with opioid receptor agonist/antagonist, serotonergic agent, bile acid regulator, which have shown promising results in clinical trials¹¹. IBS could arise from different scenario of serotonin level giving different phenotypes; such as either diarrhea, or constipation or none of these¹. This variable spectrum of IBS symptoms is the key foundation for developing various serotonin based agonist and antagonist to treat IBS. Recent serotonin transporter knock out animal model study suggests mimicking some spectrum of humanized IBS¹².

Results

Herein we report a physical stressor mediated IBS in rat model that shows alternation of serotonin receptor (5-HT_{3A}R) surface presentation in the intestine and colon. We also report that thymol treatment smooths out the IBS symptoms by altering the 5-HT_{3A}R level. Thymol, a mono terpenoid phytochemical found in Southeast

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