จุลินทรีย์โปรไบโอติกส์และความสัมพันธ์ในโรคซึมเศร้า

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บทคัดย่อ

โรคซึมเศร้าเป็นโรคทางจิตเวชที่อาจนำไปสู่ปัญหาทางจิตขั้นรุนแรงถึงขั้นการฆ่าตัวตาย ปัจจัยการเกิดโรคซึมเศร้าประกอบด้วยปัจจัยทางพันธุกรรมและปัจจัยทางสิ่งแวดล้อม ได้แก่ อายุ ความเครียด การรับประทานอาหาร และรูปแบบการดำเนินชีวิต งานวิจัยในปัจจุบันพบว่าความผิดปกติของจุลินทรีย์ในระบบทางเดินอาหารมีผลต่อการเกิดโรคซึมเศร้า โดยเกิดผ่านกลไกการสื่อสารของจุลินทรีย์ในระบบทางเดินอาหาร ฮอร์โมน ระบบประสาท และระบบภูมิคุ้มกันของร่างกาย นำไปสู่การเปลี่ยนแปลงทางด้านพฤติกรรม อารมณ์ และการหลั่งสารสื่อประสาทที่ผิดปกติ นอกเหนือจากการรักษาโรคซึมเศร้าโดยการใช้ยา ปัจจุบันมีการใช้จุลินทรีย์โปรไบโอติกส์ ซึ่งเป็นจุลชีพที่มีชีวิตและมีประโยชน์ต่อสุขภาพ เพื่อปรับสมดุลของจุลินทรีย์ในระบบทางเดินอาหารและลดผลข้างเคียงจากการใช้ยา การศึกษาในสัตว์ทดลอง อาสาสมัครสุขภาพดี และผู้ป่วยโรคซึมเศร้าพบว่าการรับประทานจุลินทรีย์โปรไบโอติกส์ส่งผลดีต่อสุขภาพจิต โดยลดความเครียด ความรู้สึกด้านลบ และภาวะซึมเศร้า สำหรับประเทศไทยอาหารไทยหลายชนิดมีคุณสมบัติของโปรไบโอติกส์ อย่างไรก็ตามงานวิจัยในเรื่องดังกล่าวต่อสุขภาพจิตไม่แพร่หลายมากนัก การทราบถึงประโยชน์ของโปรไบโอติกส์ต่อผู้ป่วยโรคซึมเศร้าจะเป็นการสนับสนุนให้มีการทำวิจัยเกี่ยวกับอาหารไทยที่มีคุณสมบัติของโปรไบโอติกส์และผลต่อสุขภาพจิตเพิ่มมากขึ้น

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Probiotic and Relation to Major Depressive Disorder (MDD)

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Abstract

Major depressive disorder (MDD) is a psychiatric disorder that leads to severe mental problem and may cause suicide. Factors that lead to depression consist of genetic factors and environmental factors such as age, stress, diet intake and sedentary lifestyle. Recent findings revealed that gut microbiome dysbiosis has an effect on MDD patients via a communication of gut microbiome, hormone, nervous system and immune system that leads to behavioral, emotional and neurotransmitter change. Probiotics are defined as living bacteria, when administered in adequate amounts, confer a health benefit on the host. Probiotics were used to adjunct therapy in MDD patients to balance gut microbiome composition and reduce side effects from antidepressant drugs. Studies in animal, healthy volunteer and psychiatric patients indicate that consumption of probiotics has mental benefits that reduce stress, negative emotion, anxiety state and depression. Many foods in Thailand have probiotic characteristics but there have been limited studies about the effect of probiotic on psychological outcomes. This review may support the benefits of probiotics in MDD patients and inspire researchers to do the study about the effect of Thai probiotic foods on emotion or psychological outcomes.

Keywords: Major depressive disorder, Gut microbiome, Probiotics

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Introduction

Depression is a common illness worldwide, more than 264 million people of all ages affected[1]. More than twice the amount of depression is detected in women. The number of depressive patients has increased in each year as to six percentage of the total population[2]. Major depressive disorder (MDD) is a common and severe mood disorder. Most patients suffer from a chronic depressed mood for at least two weeks resulted in behavior and mental change. For example, depressed mood, loss of interest or pleasure, significant weight loss, decrease or increase in appetite and recurrent thoughts of death or a specific plan for committing suicide. Moreover, individuals can also present with physical symptoms such as chronic pain or digestive problems. of depression. For diagnosis of depression, the criteria are based on the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), released in 2013. The cluster of symptoms that characterize a major depressive episode and these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning[3].

Previous study reported that the pooled estimate of risk ratio for mood disorders was 12.3 (95% CI 8.9–17.1). The pooled proportions for mood disorders in suicides and non-suicides were 11.3% and 6.8%[4]. These findings underline the important role of mental disorders in suicide and many efforts should be implemented to prevent these mental disorders including MDD. The molecular mechanisms and abnormal pathophysiological of MDD are inconclusive due to various multifactorial factors related to the disease, including genetic, epigenetic, and environmental factors. Gene-environment interaction is one of the major causes of mood disorders and it involves crucial pathways such as genetic susceptibility, epigenetic modification, neurotransmitter imbalance, abnormal of neuroendocrine metabolism, sporadic regulation of neurotrophic and the other growth factors synthesis, secretion, and signaling, oxidative stress, and chronic inflammation[3].

There are effective treatments for MDD such as behavioral activation, cognitive behavioral therapy or antidepressant medication but each treatment has limitations depending on severity of symptoms and risk of non-response to treatments. Some treatment may produce

adverse effects such as headaches, nausea, agitation, sedation, and sexual dysfunction[5]. A pivotal task in the future of MDD research will be to prevent and treat MDD with a role of nutrition such as dietary intake and overall nutritional status. As discussed in the underlying mechanisms of MDD, numerous dietary constituents are responsible for normal brain functioning, including enzymatic activity, cellular and oxidative processes, receptor function, signal transmission, maintenance of neuronal tissue, and synthesis and function of neurotransmitters and catecholamines[6].

Human gastrointestinal tract has many microorganisms, also known as gut microbiota, especially in the intestines that have 10^{14} bacterial cells, a number that is more than fourteen times compared with the total amount of cells in the human body[7]. The gut microbiota has important roles in the body e.g., contribute to digestion and absorb some nutrients that the human body can't digest, help to synthesize vitamin K and vitamin B, stimulate immune system and protect human cells from pathogens[8]. This is mediated by the gut microbiota-brain axis that lays the foundation for the intricate communicative pathways between gut microbiota and the nervous, immune and endocrine systems. If the component of microorganism is not balanced, it causes abnormal digestion and other human system pathology. Many research studies reported the causal relationship between gut microbiota and MDD. As compared to healthy individuals, patients have the number of gut microbiome phylum *Actinobacteria, Bacteroidetes, Firmiculate, Fusobacteria* and *Proteobacteria* abnormal growth[9] and using probiotics can improve gut microbiota abnormalities and depressive behaviours[10].

Probiotics are defined as living bacteria, when administered in adequate amounts, confer a health benefit on the host such as improving symptoms from lactose maldigestion, diarrhea, irritable bowel disease, protect colon cancer and boost immune system[11]. Probiotics may contain a variety of microorganisms. The most common are bacteria that belong to groups called *Lactobacillus* and *Bifidobacterium*. Other bacteria may also be used as probiotics, and so may yeasts such as *Saccharomyces boulardii*. Different types of probiotics may have different effects. For example, if a specific kind of *Lactobacillus* helps prevent an illness, that doesn't necessarily mean that another kind of *Lactobacillus* or any of the *Bifidobacterium* probiotics would do the same thing[11,12].

The aims of this review are to describe the effects of probiotics on MDD and contributing risk factors, define the role of gut microbiota-brain axis and the process by which gut brain maladaptive that leads to developing MDD and indicate the possible evidence supporting use of probiotics as adjunct therapy in depression.

MDD and risk factors

MDD results from the complex interaction between two factors, as shown in Figure 1. First, biological factors e.g., genomes, age, chemicals balance and cell communication. These factors were called non-modifiable factors. Second, environmental factors e.g., stress, diet, drug and sedentary lifestyle. These factors can change in each people, also called modifiable factors[13]. The modifiable factors, especially high fat and simple carbohydrate diets including stress, have an effect on the number of gut microbiome phylum via gut microbiota-brain axis. This mechanism refers to the network of connections involving multiple biological systems that allows bidirectional communication between gut bacteria and the brain and is crucial in maintaining homeostasis of the gastrointestinal, central nervous and microbial systems of animals[14].

Gut microbiota-brain axis

The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions[15-16]. The gut brain axis transforms information via the vagus nerve from food to feelings. Digested food particles enter the small intestine which is covered with a velvety layer of villi. Each villus is lined with a single layer of epithelium. This layer is made up of different cell types. One of them, the enteroendocrine L cells (L cells) are unlike the others. They are known to act as chemoreceptors, initiating digestive actions and detecting harmful substances and initiating protective responses. In addition to communicating through hormones, the L cells synapse with nerves including the vague nerve and nerves neuropod cells. The L cells sense and react to their environment. They sense mechanical, thermal and chemical stimuli such as nutrients, bacterial by products e.g., short chain fatty acids (SCFAs), lipopolysaccharide (LPS), secondary bile acids and neuroactives e.g.,

dopamine, norepinephrine, serotonin, etc. in the gut lumen[17]. Inside neuropod cells, signals from stimuli are converted into tiny electrical pulses. These pulses propagate via synapses on the afferent neuron of the vagus nerve. Vagul neurons carry the sensory information to the brain stem, linking the signals generated inside the small intestine to the brain. Stimulation of L cells by bile acids or SCFAs results in the release of anorexigenic hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), and can increase concentrations of peripheral hormones, such as insulin, leptin, and ghrelin that affect appetite and metabolism[18]. The neuropod cell connection with the vagus nerve serves as a conduit for food in the gut influence brain function within seconds. This connection is also a potential portal for gut pathogens to access to the brain that cause brain inflammation and abnormal brain function.

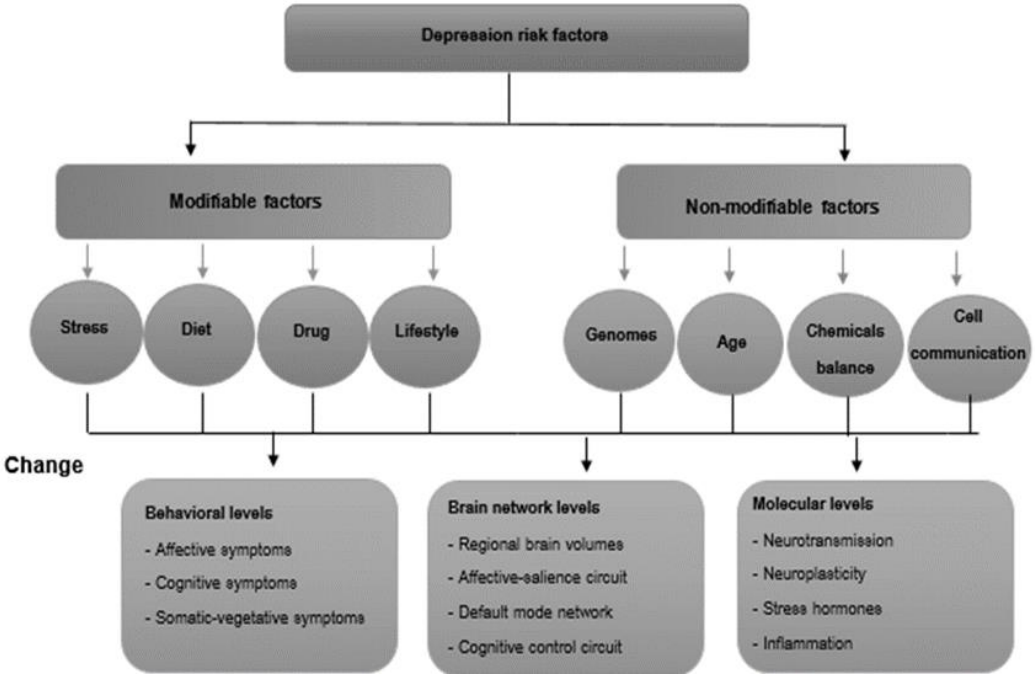

Figure 1. Risk factor related to MDD. Non-modifiable factors together with modifiable factors can support pathogenesis of MDD that cause (1) behavioral change such as decline cognitive function, increase risk to develop affective disorders or psychiatric disorders (depression and bipolar) and somatic-vegetative symptoms (e.g., weight loss, loss of appetite, insomnia, fatigue and inattention). (2) change of brain network levels affect brain volumes especially hippocampus volume, increase risk of dysfunction in the salience network, default mode network and cognitive circuit that cause brain structural and functional abnormality. (3) molecular level change such as abnormal neurotransmitters (e.g., serotonin) and stress hormone secretion, reduction of neuroplasticity can induce proinflammatory cytokine secretion which lead to brain inflammation.

The brain can modulate various functions of the gut, as well as the perception of gut stimuli, via a set of parallel outflow systems that are referred to as the emotional motor system (EMS), which include the sympathetic and parasympathetic branches of the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and endogenous pain-modulation systems. Activation of the EMS can occur via interoceptive and exteroceptive stressors. The enteric microbiota is likely to interact with gut-based effector systems and with visceral afferent pathways, which establish a bidirectional brain–gut–enteric microbiota axis[19].

Dysregulation of gut microbiota-brain axis related to depression

The human body can respond to stress via the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis[20]. In response to stress, the hypothalamus secretes corticotropin releasing hormone (CRH) to control the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH). ACTH plays an important role in stimulating the adrenal cortex to secrete cortisol hormone, which causes the sympathetic nervous system to respond. This reaction leads to stimulating the adrenal medulla to secrete epinephrine. The process by which the human body responds to stress is known as stress resilience[21-22].

Chronic stress causes stress resilience imbalance resulting in increased neuropsychiatric disorders including depression[23]. Pathogenesis of MDD has been associated with excessive stimulation of the HPA axis that causes hypothalamus to increasingly secrete CRH, which stimulates the anterior pituitary to secrete ACTH, leading to increased cortisol hormone from the adrenal cortex[24]. High levels of cortisol hormone caused by chronic stress can stimulate inflammation of the central nervous system, which reduces neurotrophin brain-derived neurotrophic factor (BDNF) levels, leading to decreased neuroplasticity and neurogenesis3. This reaction affects brain formation process[25].

In autonomic nervous system, high level of cortisol hormone increases norepinephrine secretion from adrenal cortex that stimulate inflammation. At the same time, norepinephrine over secretion leads to monoamine neurotransmitters e.g., serotonin (5-hydroxytryptamine), adrenaline and dopamine decrease[26]. For the immune

system, inflammation process reduces natural killer cell (NK cell) and lymphocyte cell productions whereas support cytokines e.g., tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). These cytokines can move via blood brain barrier and react with immune cell types resident in the brain such as astrocyte, microglia and other neurons. Previous study described an association between MDD and microglial activation. These finding suggest that in MDD had higher circulating monocyte that link to brain inflammation activation. Moreover, inflammatory state in the central nervous system can signal to digestive system via the tenth cranial nerve (vagus nerve) that lead to gut dysbiosis[27].

Inflammation and chronic stress increase the risk of noncommunicable diseases such as obesity, diabetes and cardiovascular disease so patients with long term MDD have a high risk for noncommunicable diseases. On the other hand, diabetic patients have high risk to develop MDD because they have low grade inflammation[3].

Recent findings provide strong evidence for the presence of bidirectional communication networks between the gut microbiota and the central nervous system (CNS). Stress has an effect on the gut microbiome. High levels of cortisol hormone cause gut barrier dysfunction and gut microflora reduction that promotes lipopolysaccharide (LPS) from pathogens moving through blood circulation. LPS induces proinflammatory cytokine secretion and transfers to the CNS, leading to brain inflammation. Stress also stimulates the sympathetic nervous system to secrete catecholamine neurotransmitters e.g., epinephrine and norepinephrine that have an effect on the gut microbiome and immune system, which leads to gut microbiome dysbiosis and an increase of inflammatory cells, such as monocytes expressing high levels of Ly6C (Ly6chi monocytes) and neutrophils, or of proinflammatory mediators, such as IL-1b, IL-6, and tumor necrosis factor alpha[28].

Another mechanism by which the gut microbiome affects depression is the regulation of tryptophan metabolism[29]. The beneficial bacteria indirectly impact tryptophan availability and serotonin synthesis by decreasing the activity of enzymes responsible for tryptophan degradation along the kynurenine pathway[30]. Kynurenine is produced from tryptophan by the action of the hepatic-based enzyme, tryptophan-2,3-dioxygenase (TDO) or the

ubiquitous indoleamine-2,3-dioxygenase (IDO)[31]. TDO can be induced by glucocorticoids or indeed tryptophan itself, whereas IDO is influenced by certain inflammatory stimuli. Once kynurenine is produced, it is further metabolized along two distinct arms of the pathway with one leading to the production of the neuroprotective kynurenic acid (alpha 7 nicotinic acetylcholine receptor antagonist and N-methyl-d-aspartate (NMDA) receptor antagonist at glycine site) and the other to the neurotoxic quinolinic acid (a NMDA receptor agonist)[32]. The balance between these two metabolites is important in health and disease. Kynurenic acid (KYNA), which can be neuroprotective against quinolinic acid (QUIN) induced excitotoxicity, can also induce cognitive impairment when abnormally elevated. Kynurenine formed in the periphery can cross the blood-brain-barrier and is the main source of CNS kynurenine. This is likely due to its effects on the a 7-nicotinic acetylcholine receptor[33]. Plasma kynurenine increases are thought to be a reliably reflected in the CNS[34]. The impact of increased tryptophan metabolism along the kynurenine pathway can then be viewed through the dual lens of reduced availability for serotonin synthesis and increasing the downstream production of neurotoxic/neuroprotective metabolites. Accumulating evidence implicates the gut microbiota in the regulation of kynurenine pathway metabolism. This is thus a humoral route through which the gut microbiota can influence mood and cognition at the level of the CNS as well as local gastrointestinal (GI) function.

Association between probiotic and changed in mood, stress and anxiety

Gut microbiota dysbiosis is one of the important risks MDD[35]. The use of probiotics as an alternative or adjuvant treatment for relieving symptoms of MDD, anxiety and solving gut microbiome imbalance could be a critical turning point in the management of the disorder[36]. There are effective treatments for depression such as behavioral activation, cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT), or antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). The physiological effects of most antidepressants occur immediately after administration of the drug but the therapeutic effect can take weeks or long time to become apparent in those seeking relief from symptoms. Some patients

discontinue antidepressants use because they have the side effects before the drugs start to become effective[37]. Using probiotics to improve MDD symptoms can eliminate some of these barriers for effective treatment. They are also called psychobiotics that refer to live bacteria. When ingested in appropriate amounts, they may confer a mental health benefits by affecting the microbiota of the host organism[38-39]. However, psychobiotics is a new word. A large number of studies including this article still use the word probiotics. Nowadays, many studies are finding that probiotics have mental benefits in humans and animals.

Most of MDD patients have the gut microbiome composition different from the healthy people[40]. At the phylum level, studies showed that in MDD patients have the number of gut microbiome phylum *Firmiculate, Bacteroidetes, Actinobacteria, Proteobacteria* and *Fusobacteria* abnormal growth[9]. At the family and genus level, the data from a systemic review and meta-analysis reviewed that abundances of family *Prevotellaceae* and genus *Coprococcus* and *Faecalibacterium* were decreased in MDD patient compared to non-depressant control[10]. It is unclear whether a taxon may keep a stable population within the host. It depends on genetic and environmental factors e.g., age, diet, stress, *etc*. Family *Prevotellaceae* has a major role to produce short chain fatty acid that involved to tryptophan metabolism and BDNF gene expression[41]. The research about the relationship of microbiome feature and host quality of life. Butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria were consistently associated with higher quality of life indicators. The result revealed that genus *Coprococcus* depletion in depression has relative with patient quality of life[42]. Reduction of genus *Faecalibacterium* lead to the low level of SCFA production. *Faecalibacterium prausnitzii* (ATCC 27766) supplementation in mice that were induced mild depression-like and anxiety like behavior showed significantly higher levels of SCFAs and levels of cytokines IL-10 in the plasma that prevented the effects on corticosterone, C-reaction protein and cytokines IL-6 release[43]. Randomized, doubled-blind, placebo-controlled study showed that the intake of probiotics genus *L. casei* Shirota in chronic fatigue syndrome volunteers leads to promote production of probiotics family *Lactobacillus* and *Bifidobacteria* in GI tract. In addition, volunteers who intake probiotics have anxiety symptoms less than placebo group[44].

Gut microbiota dysbiosis in depressive patients causes abnormal

neurotransmitters and neuronal proteins secretion which effect on mood and feeling. Many evidences supported that using probiotic can restore gut microbiome balance that led to improve emotional state. Studies about emotional state demonstrate that consuming yogurt or probiotics capsule have health benefits in petroleum workers. The result of emotional assessment reported that the intervention groups receive yogurt consisting of probiotics genus *Lactobacillus acidophilus* LA5 and *Bifidobacterium lactis* BB12 or probiotics capsule consist *of Lactobacillus casei, L. acidophilus, L. rhamnosus, L. bulgaricus, Bifidobacterium breve, B. longum* and *Streptococcus thermophilus* for six weeks feel happier than placebo group[45]. Study in healthy volunteers showed that intake probiotics products include *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24 and *Lactococcus lactis* W19, W5 for four weeks feel sadness less than placebo group[46]. In randomized, double-blind, placebo-controlled clinical trial in MDD patients reported that supplement probiotic capsule which consist of *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum* can improve emotional and the severity of depression[47].

Stress and anxiety are the major symptoms that found in MDD patients. These symptoms can be caused by gut microbiome dysbiosis and/or abnormal brain function to response stress. Many studies showed that supplement probiotics in healthy volunteers and MDD patients can improve stress and anxiety. Michael, et al. indicated that healthy volunteers received probiotics genus *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for thirty days can reduce anxiety symptoms and depressed feeling[46]. Another research show that using *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 can reduce psychological distress and cortisol hormone in urine. This research concludes that probiotics reduce stress by control cortisol hormone[49]. Study from meta-analysis revealed that probiotics had significant effect on depressive symptoms just in patients with depression, and no significant change in anxiety in patients, and no improvement in participant performance under stress[50].

There were some studies about probiotic in Thailand. Klayraung et al. (2008) investigated probiotic properties of *Lactobacilli* isolated from Thai traditional

food, including properties relevant to probiotic action, e.g., resistance to acid, bile tolerance, adhesive properties, antibacterial activity, and antibiotic susceptibility. From genus-specific PCR, all of selected isolates were identical to *Lactobacillus* species with various probiotic action[51]. Another study focused on the development yoghurt mixed with probiotic *L. casei* and roselle syrup and to study their properties which could be an alternative functional food for the consumers. The results showed that the survival of *L. bulgaricus, S. thermophillus* and *L. casei* decreased throughout the storage period but different levels of roselle syrup had no effect on the growth of probiotic *L. casei.* It supported that the yoghurt could be claimed for human health[52]. In addition, association between probiotic and human health were described. Tangpolkaiwalsak et al. evaluated the efficacy of probiotics supplementation in the prevention of necrotizing enterocolitis (NEC) among very low birth weight preterm infants. Infants in the study group were fed Infloran® (*Lactobacillus acidophilus* 1x109 and *Bifidobacterium bifidum* 1x109 organisms) dose 125 mg/kg/dose twice a day with breast milk or premature formula from the start of feeding until 6 weeks or discharge. There was no difference in incidence of NEC stage >2 between the two groups53. However, no reports with clinical and metabolic response to probiotic administration in patients with major depressive disorder in Thai population.

Conclusion

Probiotics treatment may improve MDD symptoms by improving gut microbiome dysbiosis, increasing neurotransmitters availability and level of neuronal proteins and/or decreasing level of inflammatory markers (Figure 2). Probiotics can be used as an alternative treatment for depression to eliminate the side effect from antidepressant medicine. A large number of studies in humans and animals indicated that probiotics consumption has mental benefits that reduce stress, negative emotion, anxiety state and depression. Although there are many Thai food that have probiotic characteristics, there have been limited studies about the effect of probiotic on psychological outcomes. In conclusion this review may support the benefits of probiotics in MDD patients and inspire researchers to do the study about the effect of Thai probiotic foods on emotion or psychological outcomes.

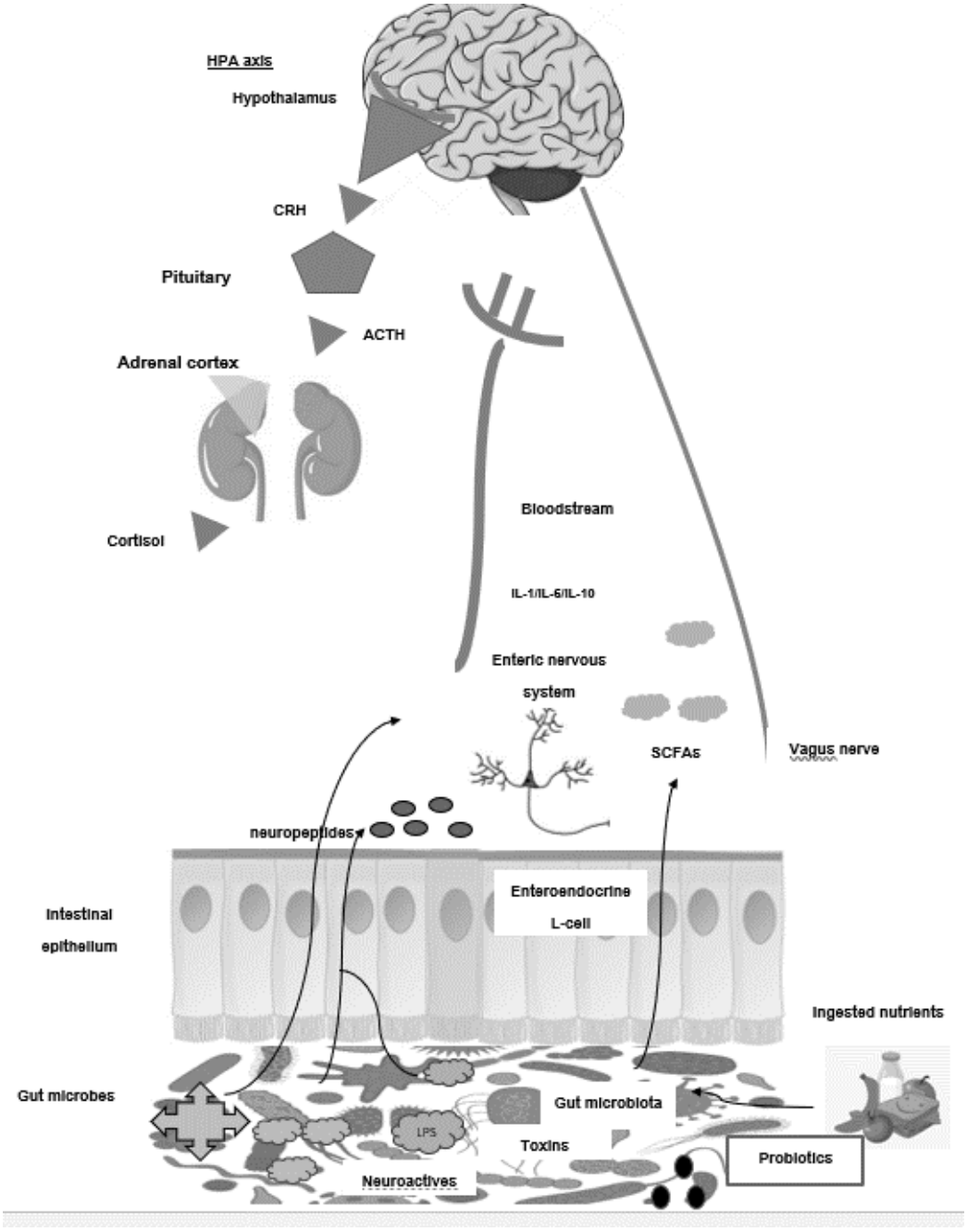

Figure 2. The brain-gut-microbiota axis in health and disease. The routes of communicate between gut and brain include neural, humoral, and immune pathways. Gut dysbiosis leads to altered immunology, activation of the HPA, and altered levels of SCFAs and tryptophan, together with aberrant signaling through the vagus nerve. Probiotics have the potential to normalize such processes. HPA = hypothalamic-pituitary-adrenal axis; SCFAs = short-chain fatty acids; CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; IL = interleukin

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Conflict of interest

The authors declare that there is no conflict of interest.

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