Major depressive disorder: Probiotics may be an adjuvant therapy

Article *in* Medical Hypotheses · February 2005

Impact Factor: 1.07 · DOI: 10.1016/j.mehy.2004.08.019 · Source: PubMed

2 authors, including:

Martin A Katzman
Start Clinic for Mood and Anxiety Disorders
69 PUBLICATIONS **1,241** CITATIONS

Medical Hypotheses (2005) **64,** 533–538

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Major depressive disorder: probiotics may be an adjuvant therapy

Alan C. Logan[a,*], Martin Katzman[b]

[a] *Nutrition Research Consulting, 50 Yonkers Terrace, 8-J Yonkers, NY 10704, USA*
[b] *Start Clinic for Mood and Anxiety Disorders, Psychiatry, University of Toronto, 790 Bay Street, Suite 900 Toronto, Ont., Canada, M5G 1N8*

Received 5 August 2004; accepted 17 August 2004

Summary Major depressive disorder (MDD) is an extremely complex and heterogeneous condition. Emerging research suggests that nutritional influences on MDD are currently underestimated. MDD patients have been shown to have elevated levels of pro-inflammatory cytokines, increased oxidative stress, altered gastrointestinal (GI) function, and lowered micronutrient and ω-3 fatty acid status. Small intestinal bacterial overgrowth (SIBO) is likely contributing to the limited nutrient absorption in MDD. Stress, a significant factor in MDD, is known to alter GI microflora, lowering levels of lactobacilli and bifidobacterium. Research suggests that bacteria in the GI tract can communicate with the central nervous system, even in the absence of an immune response. Probiotics have the potential to lower systemic inflammatory cytokines, decrease oxidative stress, improve nutritional status, and correct SIBO. The effect of probiotics on systemic inflammatory cytokines and oxidative stress may ultimately lead to increased brain derived neurotrophic factor (BDNF). It is our contention that probiotics may be an adjuvant to standard care in MDD.

Introduction

Major depressive disorder (MDD) is a recurrent, debilitating, and potentially life threatening illness. Research indicates that nutritional influences on MDD are currently underestimated [1]. Some potentially beneficial bacteria, which are lowered in states of stress and chronic illness, may potentially influence depression by a number of mechanisms. Emerging research suggests that alterations in the intestinal microflora may have immune and non-immune manifestations beyond the gastrointestinal (GI) tract. Probiotic therapy is generally defined as using beneficial bacteria to improve the intestinal microbial balance of the host. The goal of this report is to integrate various branches of research in order to support our hypothesis, that probiotic bacteria may have potential as an adjuvant therapy in MDD treatment.

Normal microflora

The human GI tract contains a complex and delicately balanced ecosystem of 500 bacterial

* Corresponding author. Tel.: +1 914 237 8058; fax: +1 914 237 8897.
E-mail addresses: aclnd@cfs-fm.org (A.C. Logan), mkatzman@startclinic.ca (M. Katzman).

0306-9877/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2004.08.019

species belonging to about 200 genera. A number of factors will determine the variety and location of bacteria in the intestines, including stomach acid secretion and small bowel motility. Two particular genera of bacteria, lactobacilli and bifidobacterium, are well documented to have beneficial effects in the human body. These bacteria are involved in vitamin synthesis, stimulation of the immune system, prevention of pathogenic and opportunistic microbial colonization, protection of the intestinal barrier defense system, production of short chain fatty acids for enterocyte energy, metabolism of carcinogenic substances and lowering levels of potentially neurotoxic components [2]. Specific strains of probiotics may alter cytokine secretion and act as potent antioxidants within and beyond the GI tract [3,4]. Emerging research also suggests that fats, and ω-3 fatty acids in particular, have a symbiotic relationship with potential probiotics [5].

Intestinal flora in MDD related conditions

While there have been no published reports on the state of intestinal microflora in human depression, there is some evidence from associated conditions where depressive symptoms are part of the picture. Approximately 30% of those with MDD have diagnosable irritable bowel syndrome (IBS). IBS patients have been shown to have decreased lactobacilli, bifidobacterium, coliforms as well as increased aerobes and a reduction of the normal anaerobe to aerobe ratio. Prior antibiotic use has been shown to be a risk factor in the onset of IBS.

Research has also connected atopic disease with an increased risk of developing diagnosable MDD (2.7-fold higher vs. controls) and attention deficit hyperactivity disorder (2.7-fold higher). While ω-3 fatty acids may be a common thread here, we suggest that altered intestinal microflora may be involved. The intestinal microflora in atopic dermatitis has been shown to contain significantly lower levels of bifidobacterium and higher levels of staphylococcus. Percentages of bifidobacteria are significantly lower in patients with severe atopy vs. those with mild symptoms [6].

Pediatric recurrent abdominal pain and infantile colic have been found to be associated with behavioral problems later in life. Functional recurrent abdominal pain in childhood predicts later anxiety and depressive disorders in adulthood. Recently, investigators reported that the levels of lactobacilli are lower in cases of pediatric colic vs. controls [7].

Chronic Fatigue Syndrome (CFS) and fibromyalgia (FM) are conditions where depressive symptoms are commonly reported. Researchers have documented lower levels of bifidobacterium and higher levels of enterococcus spp in these patients. Interestingly, it was shown that the higher the aerobic enterococcal count among CFS/FM patients, the more severe the neurological and cognitive deficits; nervousness, memory loss, forgetfulness and confusion [8]. All of these symptoms are characteristic of MDD.

Endometriosis (EM) is a condition where depressive symptoms are common, and where lactobacilli levels may be low. In four related conditions — EM, IBS, CFS and FM — a migration of bacteria from the colon into the small intestine is commonplace. The result is small intestinal bacterial overgrowth (SIBO) which has been documented in these conditions by the lactulose hydrogen breath test. Migration of bacteria into the small intestine appears is associated with higher levels of somatic pain [9]. SIBO has not been formally investigated in MDD, although it is likely to occur in these patients because it is often the result of intestinal stasis or low stomach acid secretion. Patients with depression are known to have low levels of stomach acid production and intestinal stasis. Cytokines linked to depressive symptoms, particularly interleukin 1-beta (Il-1β) and tumor necrosis factor alpha (TNFα), are capable of inhibiting gastric acid secretion. In addition, physical inactivity, common to depression, is associated with SIBO. Various strains of probiotics have been shown to be helpful in the treatment of SIBO [10].

The significance of SIBO related to depression is that not only can it account for the functional abdominal complaints in MDD, it can cause malabsorption of fat, carbohydrate, protein, B vitamins and other micronutrients. Lowered nutrient levels may in turn weaken host defense against SIBO. Patients with depression are known to have low levels of folic acid, vitamins B_{12}, B_6 and zinc [11—14]. Low levels of vitamin B_6 is associated with diminished conversion of alpha linolenic acid into mood regulating eicosapentaenoic acid (EPA). Non-digestible oligosaccharides can increase the availability of nutrients including zinc, effects that are attributed to increased bifidobacterium. It is interesting to note that treatment of SIBO has led to improvements in depression, memory and concentration among CFS patients [15].

It is also of note that Crohn's disease is a condition where depression precedes and follows diagnosis more often than expected by chance. Cognitive deficits have been observed in patients with Crohn's disease, and depression is correlated

with relapses. The microflora of those with Crohn's disease has been reported and low numbers of lactobacilli are characteristic [16].

Stress, MDD and microflora

Stressful life events are strongly associated with first onset of major depression and with subsequent episodes of MDD. The research also indicates that the relationship is, at least in part, a causal one. The influence of stress on the intestinal microflora has been the subject of some research in animals and humans. The animal studies indicate that environmental stressors can increase aerobic bacteria and decrease lactobacilli [17,18]. Restraint conditions, acoustic stress and food deprivation have all been shown to negatively alter microflora in various animal studies [19—21].

Lower lactobacilli levels have been specifically correlated with the display of stress-indicative behaviors in animals. Altered GI flora may be a result of changes in gut motility, GI acidity and/or the direct effect of neurochemicals such as norepinephrine [22]. Maternal stress during pregnancy can result in a reduction of both lactobacilli and bifidobacterium in offspring, relative to controls [23]. Measures of infant independence are correlated with infant total anaerobes, lactobacilli and bifidobacterium concentrations [23]. Experimental research indicates a strong connection between prenatal stressors and subsequent depression in offspring.

There is also evidence from human studies indicating that stress can negatively affect microflora [24,25]. Emotional stress can lead to acute and long term reductions in lactobacilli and bifidobacterium [26]. Bifidobacterium appear to be extremely sensitive to emotional stress. Restraint stress and excess physical demands can also lead to decreases in lactobacilli and bifidobacterium in humans [27].

Depression and cytokines

Elevations in pro-inflammatory cytokines such as interferon gamma (INFγ), TNFα, 1L-6 and 1L-1β have all been observed in MDD. In fact, elevations in 1L-1β and TNFα are associated with the severity of depression. Pro-inflammatory cytokines can affect mood by a number of mechanisms, including lowering of neurotransmitter precursor availability, activation of the hypothalamic-pituitary adrenal axis, and alteration of metabolism of neurotransmitters and neurotransmitter transporter mRNA [28].

Nerve growth factors, including brain derived neurotrophic factor (BDNF), can play a role in the plasticity and survival of the developed nervous system and may attenuate the depression-associated neural atrophy in the hippocampus and prefrontal cortex. BDNF is known to be lower in MDD, and has been negatively correlated with the severity of depressive symptoms [29]. Inhibition of inflammatory cytokines by antidepressants may ultimately lead to increased BDNF.

Research suggests that a substantial cytokine elevation in periphery need not be necessary for behavioral symptoms, and alterations in sleep-wake behavior may be some orders of magnitude below levels found in acute inflammation, infection and immunopathology. The evidence suggests that cytokines influence complex brain functions, even when circulating levels are very low [30].

Depression and oxidative stress

A recent human study found that depressive symptoms are independently correlated with lipid peroxidation in Japanese females. Patients with obsessive compulsive disorder (OCD) and co-morbid MDD have higher levels of lipid peroxidation than those with OCD alone. Dietary interventions are known to influence the antioxidant defense system, and the bioavailability of dietary antioxidant phytochemicals may be dependent upon the composition of the intestinal microflora [31]. ω-3 Fatty acids have been shown to decrease lipid peroxidation and antioxidant supplementation can prevent the negative influence of saturated fat on BDNF levels and cognitive function in rats.

Omega-3, lipids and microflora

Research has shown that dietary fish consumption may reduce the risk of MDD, seasonal affective disorder, bipolar disorder and post-partum depression. The epidemiological evidence is supported by a wealth of experimental and animal research. Clinical studies have demonstrated beneficial effects of ω-3 fatty acids in various psychiatric disorders. EPA has emerged as a strong candidate for the treatment of MDD [1].

In contrast to the increased incidence of depression, the dietary intake of ω-3 fatty acids has dramatically declined in Western countries over the last 100 years. This is largely a result of the ubiquitous supply of various omega-6 rich oils (corn, safflower, sunflower, cottonseed) added directly to

the food supply or through animal rearing. There is some evidence indicating that these large scale changes in dietary fat intake can significantly influence intestinal microflora, and, in turn, intestinal microflora can influence ω-3 levels.

Recent studies suggest that there are differential affects of various fat types on intestinal flora. A study involving mice was conducted using three different groups; 10% corn oil, or 1% corn oil and 9% fish oil, or 1% corn oil and 9% beef fat. The fish oil diet led to a three fold increase in bifidobacteria levels and the lowest levels of bacteroides relative to the other groups [32]. In vitro studies have shown that omega-6 rich corn oil and pure linoleic acid can specifically inhibit the growth of bifidobacteria. In contrast, pure EPA is inhibitory to human bacteroides in vitro [33]. In Arctic charr, it was found that either 4% fish oil or 7% flax oil in the diet could increase lactic acid bacteria, and lactobacilli in particular. Coconut oil was not able to raise lactic acid bacteria in the microflora [34].

Polyunsaturated fats appear to have an effect on the adhesion of probiotics to intestinal cells. Arachodonic acid causes less adhesion, while flaxseed oil causes a relative increase in adhesion to intestinal cells. Seal oil, high in EPA, has been shown to increase the adhesion of lactobacillus paracasei by 12% in the intestines [35]. Fatty acids are actually taken up inside the bacteria and have the potential to alter bacterial structure, and ultimately affect probiotic adhesion.

The relationship between ω-3 fatty acids and probiotics may be bi-directional, as research shows that bifidbacterium (Bb-12), given to atopic infants over 7 months, increases the amount of alpha-linolenic acid in the plasma phospholipids [36]. In a study involving hens, it was shown that egg EPA levels were significantly increased when a lactobacillus probiotic blend was added to flaxseed in feed vs. flaxseed alone [37].

The prevalence of MDD and seasonal affective disorder are known to be lower in Japan compared to Canada. The numbers of lactobacilli and bifidobacterium are higher in healthy Japanese adults vs. those in Canada. The effect of intestinal flora and probiotics on ω-3 status, and the influence of fish oil on intestinal bacteria certainly deserves further investigation.

Probiotics to augment treatment of depression?

The gut contains over 100 million neurons; the GI tract is ultimately a meeting place of nerves, microorganisms and immune cells. Microorganisms are responsive to the host's neuroendocrine environment and, conversely, bacteria can influence the neuroendocrine environment by the production of neurochemicals such as gamma amino butyric acid (GABA), serotonin, and various biologically active peptides.

Animal studies indicate that GI microorganisms can directly activate neural pathways, even in the absence of an immune response. Orally administered *Campylobacter jejuni*, in subclinical doses too low to elicit immune activation, can result in anxiety provoking effects in mice [38]. In addition, it has been confirmed that oral *C. jejuni* can activate visceral sensory nuclei in the brainstem, even when the bacterial counts are too low to cause an immune response. The areas of brainstem activation, nucleus of the solitary tract and lateral parabrachial nucleus, are part of a restricted set of nuclei that participate in neural information processing that can ultimately lead to autonomic, neuroendocrine and behavioral responses to bacteria [39].

Probiotic bacteria may influence mood by their effect on cytokine production. While most of the research on probiotics and cytokine release has focused on local GI effects, there is evidence of a systemic effect. Specifically, various strains of probiotics have been shown to attenuate 1L-1β, TNFα, IL-6 and INFγ beyond the GI mucosa and in the periphery [40]. Given the potential role of even low levels of these cytokines in MDD, experimental studies are warranted to determine the effect of probiotics on systemic cytokines and behavior. The systemic effect of orally administered probiotics is pronounced, capable of leading to impressive reductions in joint inflammation in arthritic rats [41]. The inhibitory effects of probiotics on inflammatory cytokines may therefore ultimately influence MDD and BDNF levels.

Probiotic therapy has been shown to improve lactose maldigestion, an important finding when considering that lactose malabsorption is associated with early signs of MDD [42]. In lactose malabsorption, high intestinal lactose concentrations may interfere with L-tryptophan metabolism and serotonin availability. Probiotics have been used successfully in controlled studies involving IBS patients [43] and can prevent rises in enterococci levels, the bacteria associated with cognitive dysfunction in CFS. Probiotics have been shown to improve well-being in patients with arthritis [44] and have been reported to reduce the side effects of antidepressant medications [45]. A combination of probiotic cultures and multivitamin/minerals has been shown to improve depressive symptoms in a group of fatigued adults under stress [46].

Additional considerations related to MDD and probiotics include the influence of beneficial bacteria on B vitamin status [47], and, as mentioned, ω-3 status and mineral absorption. The ability of probiotics to act as strong antioxidants, particularly in the prevention of lipid peroxidation [48], may have important effects in MDD. Finally, the ability of probiotics to limit SIBO [10] may have a positive influence in MDD.

Collectively, the research suggests that probiotics have the potential to act as an adjuvant in MDD treatment. The potential of probiotics and ω-3 fatty acids together is an exciting area of potential research in MDD. It is certainly clear that the microbes of the GI tract have important functions in the human body and appear to be intricately involved with the systemic immune and nervous systems. It is our contention that the role of the intestinal microflora, and the potential of probiotics in MDD, is worthy of further exploration.

References

[1] Horrobin DF. Food, micronutrients, and psychiatry. Int Psychogeriatr 2002;4:331—4.

[2] Holzapfel WH, Haberer P, Snel J, Schillinger U et al. Overview of gut flora an probiotics. Int J Food Microbiol 1998;41:85—101.

[3] Sheil B, McCarthy J, O'Mahony L, Bennett MW et al. Is the mucosa route of administration essential for probiotic function? subcutaneous administration is associated with attenuation of murine colitis and arthritis. Gut 2004;53:694—700.

[4] Kullisaar T, Songisepp E, Mikelsaar M, Zilmer K et al. Antioxidative probiotic fermented goats' milk decreases oxidative stress-mediated atherogenicity in human subjects. Br J Nutr 2003;90:449—56.

[5] Bomba A, Nemcova R, Gancarcikova S, Herich R. Improvement of the probiotic effect of micro-organisms by their combination with maltodextrins, fructo-oligosaccharides and polyunsaturated fatty acids. Br J Nutr 2002;88(Suppl.):S95—99.

[6] Watanabe S, Narisawa Y, Arase S, Okamatsu H et al. Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol 2003;111:587—91.

[7] Savino F, Cresi F, Pautasso S, Palumeri E et al. Intestinal microflora in breastfed colicky and non-colicky infants. Acta Paediatr 2004;93:825—9.

[8] Butt HL, Dunstan RH, McGregor NR, Roberts TK. Bacterial colonosis in patients with persistent fatigue. In: Proceedings of the AHMF international clinical and scientific conference, Sydney, Australia; 2001 December 1—2.

[9] Pimentel M, Wallace D, Hallegua D, Chow E et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Disease 2004;63:450—2.

[10] Gaon D, Garmendia C, Murrielo NO, de Cucco Games A et al. Effect of Lactobacillus strains (*L. casei* and *L. acidophilus* strains cerela) on bacterial overgrowth-related chronic diarrhea. Medicina (B Aires) 2002;62:159—63.

[11] Morris MS, Fava M, Jacques PF, Selhub J et al. Depression and folate status in the US population. Psychother Psychosom 2003;72:80—7.

[12] Tiemeier H, van Tuijl HR, Hofman A, Meijer J et al. Vitamin B12, folate, and homocysteine in depression: the Rotterdam study. Am J Psychiatry 2002;159:2099—101.

[13] Stewart JW, Harrison W, Quitkin F, Baker H. Low B6 levels in depressed outpatients. Biol Psychiatry 1984;19:613—6.

[14] Nowak G, Siwek M, Dudek D, Zieba A et al. Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. Pol J Pharmacol 2003;55:1143—7.

[15] Pimentel M, Hallegua D, Chow EJ, Wallace D et al. Eradication of small intestinal bacterial overgrowth decreases symptoms in chronic fatigue syndrome: a double blind, randomized study. Gastroenterology 2000;118:A414.

[16] Ott SJ, Musfeldt M, Wenderoth DF, Hampe J et al. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. Gut 2004;53:685—93.

[17] Suzuki K, Harasawa R, Yoshitake Y, Mitsuoka T. Effects of crowding and heat stress on intestinal flora, body weight gain, and feed efficiency of growing rats and chicks. Nippon Jujigaku Zasshi 1983;45:331—8.

[18] Schaedler RW, Dubos RJ. The fecal flora of various strains of mice: its bearing on their susceptibility t endotoxin. J Exp Med 1962;115:1149—60.

[19] Tannock GW, Savage DC. Influences of dietary and environmental stress on microbial populations in the murine gastrointestinal tract. Infect Immun 1974;9:591—8.

[20] Vikha GV, Liz'ko NN, Korol'kov VI, Rykova MP et al. Carbohydrate adaptive substance for prophylaxis of immune disorders and correction of dysbacterioses. Aviakosm Ekolog Med 1998;32:21—5.

[21] Timoveyev I, Loseva E, Alekseeva T, Perminova N. Stability to sound stress and changeability in intestinal microflora. Eur Psychiatry 2002;17(Suppl. 1):200.

[22] Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol 1999;35:146—55.

[23] Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of the gut in infant monkeys. J Pediatr Gastroenterol Nutr 2004;38:414—21.

[24] Moore WE, Cato EP, Holdeman LV. Some current concepts in intestinal bacteriology. Am J Clin Nutr 1978;31(Suppl.):S33—42.

[25] Holdeman LV, Good IJ, Moore WE. Human fecal flora: variation in bacterial composition within individuals and a possible effect of emotional stress. Appl Environ Microbiol 1976;31:359—75.

[26] Lizko NN. Stress and intestinal microflora. Nahrung 1987;31:443—7.

[27] Lizko NN. Problems of microbial ecology in man space missions. Acta Astronaut 1991;23:163—9.

[28] Suarez EC, Krishnan RR, Lewis JG. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. Psychosom Med 2003;65:362—8.

[29] Shimizu E, Hashimoto K, Okamura N, Koike K et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 2003;54:70—5.

[30] Pollmacher T, Haack M, Schuld A, Reichenberg A et al. Low levels of circulating inflammatory cytokines — do they

affect human brain functions?. Brain Behav Immun 2002;16:525–32.
[31] Manach C, Scalbert A, Morand C, Remesy C et al. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79:727–47.
[32] Kuda T, Enomoto T, Yano T, Fujii T. Cecal environment and TBARS level in mice fed corn oil, beef tallow and menhaden fish oil. J Nutr Sci Vitaminol (Tokyo) 2000;46:65–70.
[33] Thompson L, Spiller RC. Impact of polyunsaturated fatty acids on human colonic bacterial metabolism: an in vitro and in vivo study. Br J Nutr 1995;74:733–41.
[34] Ringo E, Bendiksen HR, Gausen SJ, Sundsfjord A et al. The effect of dietary fatty acids on lactic acid bacteria associated with the epithelial mucosa and from faecalia of arctic charr, salvelinus alpinus (L.). J Appl Microbiol 1998;85:855–64.
[35] Bomba A, Nemcova R, Gancarcikova S, Herich R et al. The influence of omega-3 polyunsaturated fatty acids (omega-3 pufa) on lactobacilli adhesion to the intestinal mucosa and on immunity in gnotobiotic piglets. Berl Munch Tierarztl Wochenschr 2003;116:312–6.
[36] Kankaanpaa P, Yang B, Kallio H, Isolauri E. Influence of probiotic supplemented infant formula on composition of plasma lipids in atopic infants. J Nutr Biochem 2002;13:364–9.
[37] Pheko LG, Chavez ER, Lague PC. Effects of feeding flaxseed and probiotic supplementation to layers on egg composition and fatty acids. McGill Univ Dept Animal Sci, Res Rep 1998;1:67–70.
[38] Lyte M, Varcoe JJ, Bailey MT. Anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation. Physiol Behav 1998;65:63–8.
[39] Gaykema RP, Goehler LE, Lyte M. Brain response to cecal infection with Campylobacter jejune: analysis with Fos immunohistochemistry. Brain Behav Immun 2004;18: 238–45.
[40] Ghosh S, van Heel D, Playford RJ. Probiotics in inflammatory bowel disease: is it all gut flora modulation?. Gut 2004;53:630–2.
[41] Baharav E, Mor F, Halpern M, Weinberger A. Lactobacillus GG bacteria ameliorate arthritis in Lewis rats. J Nutr 2004;134:1964–9.
[42] Ledochowski M, Sperner-Unterweger B, Fuchs D. Lactose malabsorption is associated with early signs of mental depression in females: a preliminary report. Dig Disease Sci 1998;107:1707–14.
[43] Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2001;13: 1143–7.
[44] Hatakka K, Martio J, Korpela M, Herranen M et al. Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis – a pilot study. Scan J Rheumatol 2003;32:211–5.
[45] Kline MD, Koppes S. Acidophilus for sertraline-induced diarrhea. Am J Psychiatry 1994;151: 1521–2.
[46] Gruenwalk J, Graubaum HJ, Harde A. Effect of a probiotic multivitamin compound on stress and exhaustion. Adv Ther 2002;19:141–50.
[47] Rong N, Selhub J, Goldin BR, Rosenberg IH. Bacterially synthesized folate in rat large intestine is incorporated into host tissue foly1 polyglutamates. J Nutr 1991;121:1955–9.
[48] Lin MY, Yen CL. Inhibition of lipid peroxidation by Lactobacillus acidophilus and Bifidbacterium longum. J Agric Food Chem 1999;47:3661–4.