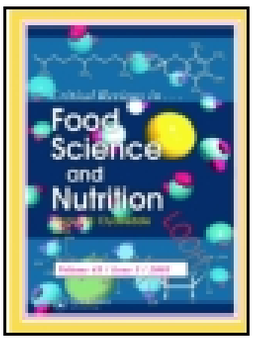

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An Overview of the Effect of Probiotics and Exercise on Mood and Associated Health Conditions.

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Abstract

The present paper provides a review of the current knowledge relating to the health benefits of probiotics, specially focused on the effects they may have together with physical exercise on mood disorders and related chronic medical conditions. With both these conditions being a substantial contributor to the global disease burden any alternative therapy must be considered. Probiotics influence the gut microbiota through a complex network of events which can influence mechanisms leading to development of mood disorders such as depression and anxiety. Similarly, through a complex interaction between psychological and neurobiological mechanisms, exercise has been found to play a key role in mood enhancement.

Keywords

Probiotics, gut microbiota, chronic disease, exercise, obesity

Background

At birth, the sterile human gut is immediately colonised with several types of microorganisms from both the mother and the environment. This results in each individual developing a unique bacterial profile by the time they reach one year of age (Forsythe et al., 2010). The distinct microbiome of each individual adult is determined through interactions between sex, genetics, diet, immune status, infection, GI disorders, antibiotics and drugs with the adult human GI tract comprised of at least 160 different bacterial species from a pool 1000-1150 (Qin et al., 2010; Marik, 2012). Within the pool there are neutral and pathogenic bacteria species alongside probiotic bacteria which prevail in a healthy gut (Desbonnet et al., 2008; Messaoudi et al., 2011).

Probiotic bacteria are live microorganisms known as 'friendly' gut bacteria which when present and/or administered in adequate amounts can have potential health benefits to the host organism (WHO, 2001; Van Baarlen et al., 2011; Bravo et al., 2012; Pyne et al., 2014).

The health benefits of 'probiotic bacteria' have been recognised for several hundred years (Jankovic et al., 2010), with the earliest record from 76 BC where Roman historian Plinio described how fermented milk could be used as a therapy for GI disturbances (Bottazzi, 1983). However, it wasn't until the invention of the microscope that microorganisms and bacteria were discovered. At the turn of the 20th century, Elie Metchnikoff suggested that fermented milk could suppress the growth of proteolytic bacteria and in turn reduce putrefaction in the gut and so prolong the lifespan of the host (Metchnikoff, 1907). Following this discovery, lactic acid bacteria and other bacteria began to be added to drugs used to treat diarrhoea and to food products to promote intestinal health and disease prevention (Jankovic et al., 2010).

Within contemporary society, probiotic bacteria are widely used for health promotion and health improvement (Ohashi and Ushida, 2009). Naturally occurring probiotic bacteria exist in fermented food products such as yoghurt, kefir, sauerkraut, cabbage kimchee and soy bean based miso and natto (Nichols, 2007). However, food supplements generally in the form of cultured dairy products which have added probiotic bacteria are now widely available to consumers. Also more recently within the consumer market 'probiotic shots' have been developed whereby probiotics can be consumed as a capsule. Contained within these food supplements there can be many strains of lactic acid bacteria; however, the most common strains belong to the species *Lactobacillus sp.* and *Bifidobacterium. sp* (Benton et al., 2007), both of which have demonstrated health benefits on the human body (Logan et al, 2003). In this sense, both these bacterial strains are known to be involved in essential physiological functions such as the stimulation of immune response, the prevention of pathogenic and opportunistic microbial/bacteria colonization, the production of short chain fatty acids, metabolism of carcinogenic substances and the synthesis of vitamins such as B and K (Logan et al., 2003).

As outlined by West et al., (2009) there are a number essential criteria for bacteria to be classified as a probiotic. As research progresses these will continue to evolve, however, the current criteria are as follows:

1. Viability during processing, transport and storage.

2. Ability to survive gastric transport.

3. Ability to adhere to and colonise the GI tract.

4. Ability to antagonise pathogenic bacteria.

5. Demonstration of clinical health outcomes

The proposed health benefits of probiotics are widespread with scientific interest in the area continually growing (Kechagia et al., 2013). However, the focus of the present paper will be on the influence of probiotics on chronic medical conditions and mood disorders. This is due to the prevalence of chronic disease and mood disorders greatly increasing in recent years. This is particularly pertinent in developed countries as a consequence of modern lifestyles. In this context the World Health Organisation estimated that globally 350 million people suffer from depression making it the leading cause of disability worldwide and so a substantial contributor to the global health burden (WHO, 2015). Furthermore, 63% of all deaths worldwide (36 million people) in 2008 were due to non-communicable diseases primarily caused by chronic illness such as diabetes, cancer and cardiovascular and respiratory diseases (Alwan et al., 2010). With the prevalence of chronic medical conditions and mood disorders continually rising, it is essential to develop any potential therapy to fight against these diseases.

Furthermore, there is also substantial evidence supporting the co-morbidity of mood disorders and chronic medical conditions (Forsythe et al., 2010). For example, Basu et al. (2004) and Heiskanen et al. (2006) have demonstrated the existence of high rates of obesity, hypertension, dyslipidaemia, metabolic syndrome and diabetes in individuals with depression. All the aforementioned symptoms are also linked to a lack of physical activity which was again associated with de development of mood disorders (Ströhle, 2009). Therefore, the aim of this review is to evaluate the literature currently available regarding the use of alternative therapies

such us the application of probiotics and exercise to reduce the prevalence of chronic medical conditions and mood disorders in the population.

The effect of probiotics on chronic medical conditions

Irritable bowel syndrome (IBS)

Approximately 30% of individuals with major depressive disorder have diagnosed IBS which is known to cause a reduction in intestinal *Lactobacilli* and *Bifidobacteria* (Logan and Katzman, 2005). The 'old friends hypothesis' suggests that one factor leading to the rise of IBS in modern society is the decreased exposure to mud, animals and faeces. This has consequently led to less contact with microorganisms which play a vital role in developing human immunoregulatory responses (Rook et al., 2012). Therefore, the rise in chronic inflammatory diseases such as IBS can be explained in developed countries partly due to changes in the microbial environment and partly due to the absence of beneficial bacteria which have the capacity to suppress the inflammatory response (Conlon and Bird, 2015). In this way increased levels of inflammatory cytokines are common in various mental health conditions and can produce symptoms of anxiety and depression (Rao et al., 2009) with some risk factors including obesity, psychosocial stress, social isolation and sedentary lifestyle (Rook et al., 2012). Therefore, if probiotics are able to decrease inflammatory cytokines and consequently IBS symptoms in humans (Lee & Da Bak, 2011), it can be hypothesised that probiotic consumption could have a positive effect on mood (Logan et al., 2005).

Chronic fatigue syndrome

Chronic fatigue syndrome is a complex illness which is poorly understood. In addition to periods of persistent fatigue, approximately 50% of sufferers are affected by anxiety or major depressive disorder (Rao et al., 2009). Furthermore, many chronic fatigue syndrome patients also have complaints of GI disturbances with over 50% diagnosed with IBS (Whitehead et al., 2002) and subsequently have reduced levels of *Bifidobacteria* and elevated levels of aerobic bacteria such as *Enterococci* (Logan et al., 2003). Therefore, if probiotics have a positive effect on mood disorders and IBS, there is the potential for them to be beneficial as an adjunctive or alternative therapy for sufferers of chronic fatigue syndrome.

Common symptoms of chronic diseases

Individuals who are affected by medical disorders such as IBS and chronic fatigue syndrome are affected by a number of common symptoms including pain, fatigue, sleep, memory and mood issues (Lakhan and Kirchgessner, 2010). These symptoms are also common in sufferers of fibromyalgia (a chronic disorder characterized by widespread musculoskeletal pain) and endometriosis (a disease in which tissue that normally grows inside the uterus grows outside it with symptoms of pelvic pain and infertility) (Sinaii et al., 2002). In particular individuals suffering from these disorders frequently have a migration of bacteria from the colon to the small intestine causing a small intestinal bacterial overgrowth (a condition where colonic bacteria expand to include the small intestine). This is associated with greater levels of somatic pain which is regularly associated with symptoms of depression (Pimentel et al., 2004). Although small intestinal bacterial overgrowth has not been investigated in those patients with major depressive disorder, Logan and Katzman (2005) have hypothesised that it is likely to occur in

these individuals due to low levels of stomach acid which can lead to small intestinal bacterial overgrowth. In this situation probiotics are a potential treatment, which may have a consequential positive effect on mood (Gaon et al., 2002).

Probiotics and the microbiota

The various inflammatory and metabolic disorders described above may be a result of dysbiosis i.e. disruption in the interactions between microbes and the host (Hemarajata and Versalovic, 2012). Probiotics may be able to partially restore the host's microbiota through various mechanisms. Bravo et al., (2012) have provided an overview of the mechanisms by which probiotics are thought to work:

- Displacement of pathogens
- Competition of metabolic interactions with hostile bacteria
- Production of bacteriocins (proteinaceous toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strains)
- Inhibition of bacterial translocation
- Enhancement of mucosal barrier function
- Effects on calcium dependant potassium channels in intestinal sensory neurons
- Induction of opioid and cannabinoid receptors in intestinal epithelial cells

- Modulation of the immune system through signals on epithelial cells and gut-associated lymphoid tissue

Probiotic bacteria are able to displace pathogens through the production of antimicrobial agents which supress the growth of other microorganisms (O'Shea et al., 2011) or through competing with other microbes on the intestinal mucosa for binding sites and receptors (Collado et al., 2007). Enhancement of mucosal barrier function via the action of probiotic bacteria may result in improved immune function. For example, *Lactobacillus sp.* has been found to improve barrier function due to decreased translocation of bacteria across the mucosa and disease phenotypes such as IBS (Lee and Da Bak, 2011). However, further studies on humans are needed to enhance our understanding of the processes involved in disease phenotypes such as IBS.

Mechanisms by which probiotics may influence mood

Probiotic bacteria work through a very complex network of events. There is compelling evidence to suggest that there is involvement of both anatomical connections such as the vagus nerve and humoral components such as the immune system and hypothalamus-pituitary-adrenal (HPA) axis (Bravo et al., 2012).

When the HPA axis is activated corticotrophin-releasing factor (CRF) is released from the hypothalamus, adrenocorticotrophic hormone (ACTH) from the pituitary and cortisol from the adrenal glands (Cryan and Dinan, 2012). Evidence suggests that an impaired HPA system is a factor linked to both depression and stress (Belmaker and Agam, 2008). Sudo et al., (2004) investigated the role of the HPA axis in development of stress in mice and found that restraint

stress in germ-free mice caused an inflated rise in ACTH and corticosterone. However, they found that this response was able to be reversed by *Bifidobacterium.*

The vagus nerve plays a key role in modulation and communication between bacteria, gut and brain, also known as the microbiota-gut-brain axis (Desbonnet et al., 2009). This axis allows bidirectional communication whereby the brain can functionally affect the gut and the gut can mediate changes in the central nervous system (CNS) (Mayer et al., 2006). Any dysfunction or alteration of the axis can have pathophysiological effects (Cryan and Dina, 2012) which may be involved in modulating various factors including pain perception, emotion and general well-being (Rhee et al., 2009). In this sense, Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS and is involved in regulating many physiological and psychological processes. Therefore, any alterations in GABA receptor expression can result in symptoms of depression or anxiety (Bravo et al., 2012).

The importance of the vagus nerve in communicating changes in the GI to the CNS has been shown in rodents whose vagus nerve was cut. For example, a strain of probiotic, *Lactobacillus rhamnosus (JB.1),* was found to reduce stress-induced elevation in corticosterone; however, these effects were not evident in the vagotomised mice (Bravo et al., 2012). This provides further evidence to support the use probiotics as a therapeutic alternative to reduce mood disorders such as stress, anxiety and depression. It is important to note that this is a brief overview of the mechanisms involved; however, within the literature the various mechanisms and pathways are discussed in greater detail e.g. Bravo et al., (2012).

The effect of probiotics on mood disorders

In recent years there has been a substantial increase in the number of studies investigating the effects of probiotics on various mood disorders. However, the idea that probiotics may improve certain mental health disorders is not a novel concept but rather one which has been recognised for several decades. For example, in 1910 it was reported that live lactic acid bacteria improved symptoms of depression in adults with melancholia (Philips, 1910). A selection of more recent work relating to probiotics and mood disorders are outlined below. The reader should be aware that a number of the more invasive studies have, to date, only been carried on in animals, therefore the applicability to humans needs to be taken into consideration.

Human studies

As outlined previously, there is an established link between chronic constipation and mood scores. In this sense, Benton et al. (2001) investigated the impact of consuming a probiotic on mood and cognition with results suggesting that more frequent constipation was associated with a poorer mood state. There was also found to be an inverse association between constipation and feelings of calmness, elatedness and agreeableness. However, the correlational nature of data prevented the conclusion of a causal relationship between constipation and mood state. Due to the continual speculation that probiotics may be a valuable adjuvant therapy for those with major depressive disorder in a more recent study the same group of authors investigated the effect of a fermented milk drink containing *Lactobacillus casei* probiotic bacteria on mood and cognition (Benton et al., 2007). Again it was suggested that reduced constipation may play a role in improving mood disorders. However, daily ingestion of the probiotic, for a period of three weeks, failed to show any improvement in mood or an increase in the number of motions passed.

The authors suggested that the lack of improvements may be related to the participants having a 'good' baseline mood with low levels of constipation (Benton et al., 2007).

However, there are a number of studies which have found a significant improvement in mood disorders with the consumptions of probiotics. For example, a six month study investigating the effects of a probiotic multivitamin compound on adults suffering from stress or exhaustion was conducted by Gruenwald et al., (2002). The overall conclusion to emerge from the study was that the multivitamin compound significantly improved the general condition of those who participated in the study with a 41% improvement in stress, a 29% decrease in the prevalence of infection and a 91% reduction in GI discomfort. Rao et al. (2009) investigated the effects of a lactic acid probiotic in patients with chronic fatigue syndrome and associated depression and anxiety. The experimental group consumed a probiotic containing a strain of *Lactobacillus* three times per day for eight weeks and compared to the placebo group were found to have a significant improvement in anxiety scores alongside an increase in faecal *Bifidobacteria* and *Lactobacillus* (73.7% and 73.7%). The changes in depression scores were not found to be significant. Similarly, Steenbergen et al., (2015) investigated the effect of a multispecies probiotic on cognitive reactivity to sad mood. The participants in this study were not diagnosed with having a mood disorder, however, it was found that those who consumed the probiotic over a four week period significantly reduced their cognitive reactivity to sad mood. The findings obtained in this study are important due to the risk of sad mood developing into clinical depression (Scher et al., 2005).

The psychotropic properties of a probiotic formulation has been assessed in both rats and humans by Messaoudi et al., (2011). The main finding to emerge from this study was that consumption of the probiotic formula containing a combination of *Lactobacillus helveticus R0052 and Bifidobacerium Longum R0175* mitigated psychological distress in three tests without displaying any adverse events. In humans, the formula was taken for 30 days and resulted in significant improvements on scales used to measure depression, anxiety and hostility. It is suggested that the effects of probiotics on anxiety and depression may have been due to competitive exclusion of detrimental gut pathogens, decreases in pro-inflammatory cytokines and communication with the CNS via vagal sensory fibres, leading to changes in neurotransmitter levels or function.

Although, there are limited human studies which have investigated the use of probiotics in the treatment of mood disorders, the current evidence suggests that it would be naïve to rule out the use of probiotics as an adjunctive therapy (Foster and McVey Neufeld, 2013).

Animal studies

Regarding animal studies, the potential antidepressant properties of *Bifidobacteria infantis* in rats were investigated by Desbonnet et al. (2009). It was found that chronic administration of the probiotic protected the rats from depressive symptoms caused by stress induced through maternal separation. The results of this study suggested that probiotics may be a suitable alternative to tryptophan supplement as a therapy for depression, although the authors highlight that these findings are preliminary and further investigation would be required to establish precise mechanisms.

Alternatively, administering a pathogenic bacteria to healthy mice has been shown to stimulate anxiety behaviours within hours of infection suggesting that changes in the gut microbiota can very quickly induce biochemical changes in the CNS (Lyte et al., 2006; Goehler et al., 2008). This highlights that altering the gut microbiota can have an effect on animal behaviour and so providing further evidence for the existence of the microbiota-gut-brain-axis (Bravo et al., 2012).

Despite not being conclusive, in short both animal and human studies, present a significant claim for the use of probiotics as an alternative treatment, particularly in those individuals with pre-existing mood disorders.

The effect of exercise on mood disorders and chronic medical conditions

There is a well-established link between physical inactivity and the risk of various non-communicable diseases which coincides with an increased prevalence of mood disorders (Goodwin, 2003). Both epidemiological and clinical studies have shown that there is a correlation between physical activity levels and prevalence of mood disorders, with physical activity generally having a positive effect on mood (Ströhle, 2009).

In this context, there are several studies where this link between physical activity and depression is evident. For example, a longitudinal study conducted by Paffenbarger et al., (1994) over 25 years found a negative correlation between physical activity levels in men and depression. This is in agreement with the findings of Motl et al., (2004) who found naturally occurring changes in physical activity levels in adolescents was inversely related to depressive symptoms.

Over the last 10-15 years there has been an increase in the number of controlled studies investigating the effects of prescribed exercise as a therapy for depression and other mood disorders. For example, Dunn et al., (2005) investigated the effects of various aerobic exercise protocols on mild to moderate major depressive disorder in adults aged 20-45 years old. The authors were able to conclude that exercise prescribed in a dosage aligned with public health recommendations was an effective treatment for mild to moderate symptoms of major depressive disorder and that greater energy expenditure is associated with larger decreases in symptoms of depression. Furthermore Blumenthal et al., (1999) concluded in their study that an exercise training programme for older adults with major depression was as effective as administering an antidepressant treatment and had a lower relapse rate.

Additional support for the role of physical activity in mood enhancement comes from a study where participants attended a regular exercise class for three months. It was found that improvements in mood were significantly greater in those individuals who had reported symptoms of depression prior to beginning the physical activity programme (Lane and Lovejoy, 2001).

Although there is a well-established association between exercise and mood enhancement, the physiological mechanisms underlying the relationship between mood and exercise are poorly understood. Despite the lack of clarity, it is likely that the mechanisms for exercise induced improvements in mood is a complex interaction between psychological and neurobiological mechanisms (Strohle, 2009). Evidence suggests that exercise decreases inflammation which in turn reduces the activity and expression of the enzyme indoleamine 2,3-dioxygenase, which

degrades tryptophan (an essential amino acid needed for the production of serotonin) (Gostner et al., 2015). Consequently, this allows for increased levels of tryptophan which when transported to the brain can increase the production of 5-hydroxytryptomin which may subsequently lead to an increase in mood state (Strasser and Fuchs, 2015).

In an attempt to gain a greater understanding of the relationship between mood and exercise, Poole et al., (2011) investigated the effects of exercise withdrawal on mood and inflammatory cytokine response. Two weeks of exercise withdrawal in healthy participants resulted in significant increase in negative mood. This was found to be significantly related to a decrease in circulating interleukin (IL)-6 (inflammatory marker), indicating that inflammatory pathways do play a role in the development of mood disorders.

Finally, even if physical activity was not found to enhance mood, it should always be recommended both to combat the various chronic medical conditions previously mentioned and simply maintain a healthy lifestyle to prevent disease.

The role of the gut microbiota in obesity

There is considerable evidence which has emerged from obesity studies highlighting the link between diet, obesity and a 'healthy gut microbiota' (Marik, 2012). Obesity is a worldwide epidemic in both adults and children and is one of the major health concerns within society. It can be largely attributed to an unhealthy lifestyle consisting of an over-abundance of energy dense food and physical inactivity. However, there is now compelling evidence suggesting that there are differences in the gut microbiota of obese and lean individuals. This fact brings to light the possibility that the development of obesity and other metabolic diseases may be influenced in

some way by the gut microbiota (Marik, 2012; Serino et al., 2012). It is also is interesting to note that there has been a correlation found between diet and the prevalence of specific bacteria groups. For example, a diet high in inulin and related fibres has been shown to increase *Bifidobacteria* (Marik, 2012). This suggests that diet can change both the composition and activity of the microbiota and thereby possibly having a positive impact on mood disorders.

Furthermore, Backhed et al. (2004) investigated the role of the gut microbiota in the regulation of fat storage in mice and found that germ-free mice had 40% less body fat compared to conventionally reared mice; despite the germ-free mice consuming more food. However, when the microbiota was harvested from the distal intestine of the normal mice and transplanted into the germ-free mice, this resulted in a 60% increase in body fat content within two weeks. From the results of the study, it was proposed that the microbiota promotes monosaccharide absorption resulting in *de novo* hepatic lipogenesis. It was therefore concluded that the gut microbiota is an important environmental factor which can affect energy storage of the host organism (Backhed et al., 2004).

The role of the gut microbiota in the development of obesity in humans has been demonstrated by Kalliomaki et al., (2008). Investigation of the faecal matter of children revealed that *Bifidobacteria* content was higher in those children of a normal weight than those who were showing signs of becoming overweight. These results suggest that there could be a possibility that consumption of *Bifidobacteria* to manipulate the gut microbiota may have a consequential positive effect on weight control in humans.

On consideration of the preceding evidence it can be suggested that the gut microbiota may influence metabolism and consequently have an impact on energy storage. This is turn may be linked to the development of chronic medical conditions such as type II diabetes and obesity, where there is significant evidence for co-morbidity with mood disorders (Turnbaugh et al., 2006).

Conclusion

The potential health benefits of probiotics and exercise are widespread. Probiotics have been found to positively influence the host microbiota. Through various mechanisms, enhancement of the gut microbiota can consequently have a positive effect on chronic medical conditions and mood disorders. The beneficial effects of exercise on chronic medical conditions are well-established. However, there is also a growing body of evidence that exercise is an effective treatment for mood disorders with recent research suggesting that these positive effects are related to the role exercise has in modulating inflammatory pathways.

Based on the evidence presented, it seems reasonable to advocate the use of probiotics and exercise as alternative therapies in the treatment of mood disorders and chronic medical conditions. However, it is important to realise the various strains of probiotics elicit different effects and may not have the same effect on everyone. It is possible that, in general, probiotics may be more beneficial for older adults who have less 'good' bacteria in their gut (Tiwari et al., 2012). Exercise protocols should be developed on an individual basis to optimise adherence to the programme.

In terms of both psychological and physiological health maintenance it is recommended for individuals to exercise regularly, eat a balanced diet high in fibre and possibly supplement with probiotics containing strains of *Lactobacilli and Bifidobacteria.*

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