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Review

Can probiotics and prebiotics contribute to healthy ageing?

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Abstract. Probiotics and prebiotics have been the subject of extensive investigations into their role in human health including their effects on risk of age-related chronic diseases. There is good evidence that probiotics and, to a lesser extent prebiotics, can influence immune function in older subjects and counteract immunosenescence and increased inflammation. Probiotics have also been shown to increase the effectiveness of influenza vaccination in the elderly and reduce risk and/or duration of upper respiratory tract infections. Prebiotics and probiotics have been shown to have benefits for common gastrointestinal disorders that are common in older people, especially constipation, and there is some evidence that symptoms of metabolic syndrome can be alleviated by certain probiotics.

Keywords: Probiotics, prebiotics, gut microbiota, immune function, gut health, inflammation

1. Introduction

Over the course of the 20th century, improvements in hygiene, sanitation, nutrition, health care, vaccinations and medical advances in treatment of diseases, have contributed to a continual increase in life expectancy in developed and developing countries [1]. A consequence of this greater lifespan is an increased prevalence of chronic degenerative diseases such as cardiovascular disease, cancer, dementia and diabetes.

Underlying these age-related changes in morbidity are changes in physiology, metabolism, inflammation(‘inflammaging’) and immune function (‘immunosenescence’) as well as changes at the cellular and molecular levels [2].

At the forefront of approaches to reduce the risk of age-related diseases and disorders and thereby improve healthy life expectancy have been dietary strategies, such as adoption of healthful dietary patterns like the Mediterranean and Okinawa diets and the development of so-called functional foods. Notable among the latter are probiotics and prebiotics. Probiotics have been defined as ‘Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [3, 4]. The majority of probiotics are strains of lactobacilli and bifidobacteria. The current consensus definition of a prebiotic is ‘a substrate that is selectively utilized by host microorganisms conferring a health benefit’ [5], important examples include fructo-oligosaccharides, galacto-oligosaccharides and inulin.

There is extensive evidence that the gut microbiota plays an important role in development and maintenance of the immune system and also the risk and/or development of several gastrointestinal and systemic diseases and disorders [6]. Situations in which the normal ecology of the gut microbiota is compromised can have serious short-term and long-term consequences. For example, treatment with broad spectrum antibiotics can severely disrupt the composition of

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the microbiota and allow overgrowth of the pathobiont *Clostridiodes difficile,* resulting in diarrhoea and mucosal damage, especially in the elderly. Irritable bowel syndrome (IBS) is a chronic disorder with a wide range of symptoms that can be debilitating. A major risk factor for IBS is a previous gastrointestinal infection with, for example *Salmonella* or *Campylobacter,* resulting in disturbance to the structure and functions of the microbial community [7]. The role of the microbiota in the development of systemic disorders such as obesity, type 2 diabetes and metabolic syndrome has been intensively studied in recent years, with differences in microbiota composition being reported between lean and obese subjects and between diabetic patients and healthy controls [8–10]. However it has proved difficult to established causal relationships and to identify specific organisms involved due to the diversity of results obtained. It is becoming increasingly clear that the metabolic capacities of the gut microbiota are potentially more important to host health than its detailed microbial composition. Of particular interest here is the production of short chain fatty acids (acetic, propionic and butyric) which have been shown to favourably affect a range of cellular and physiological processes. These include strengthening the gut mucosal barrier, acting on the gut brain neural axis to influence appetite, energy expenditure, and insulin sensitivity and, importantly for long term health, influencing and interacting with G-protein receptors with implications for suppression of inflammation, a critical mediator of metabolic and gut diseases [11–13]. Finally, it is noteworthy that numerous studies have reported differences in the microbiota of older vs younger subjects and between elderly people in care homes or living independently [14], suggesting that detrimental changes in microbiota may underly susceptibility to age related diseases.

The ability of probiotics and prebiotics to counteract the changes in microbiota or their function is a potential mechanism for their beneficial effects. The origins of probiotics as health promoting dietary components lie in the early observations by Metchnikov [15]. In studies of Caucasian peasants, he associated their longevity with their consumption of fermented milk products containing *Lactobacillus* strains and proposed that the latter suppressed the production of toxins by pathogenic bacteria in the colon. There is currently little epidemiological evidence that consumption of fermented milk products or probiotics is linked to improvements in lifespan of humans, although there are reports of effects in the *Caenorhabditis elegans* model of ageing [16]. However, there are extensive studies, particularly on probiotics, indicating beneficial effects on disease and disorders associated with old age, thus having a potential impact on healthy lifespan. The strongest evidence comes from the areas of immune function and inflammation, gut health, and respiratory tract infections.

2. Immune function

It is well established that immune function becomes compromised as people age, a process known as immunosenescence. The age-related changes include decreases in the numbers of T cells in peripheral blood, reduced ability of T cells to proliferate and secrete cytokines, a decline in innate immunity, especially natural killer (NK) cell activity and phagocytosis and a reduction in specific antibody responses [17]. These changes may underly the increased susceptibility of older people to infections of respiratory tract and the gut, as well as cancer.

There is some evidence that several probiotic strains and to a lesser extent the prebiotics fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are useful in improving the immune response, with beneficial effects on phagocytic and NK cell activity and salivary IgA excretion and dendritic cells [18, 19]. For example, a randomized, double blind, placebo-controlled trial in healthy older volunteers with *Lactobacillus casei* Shirota strain by Dong et al. [20] demonstrated a significant increase in NK cell activity and a tendency to a more anti-inflammatory cytokine profile. Similarly, a trial of *Bifidobacterium lactis* HN019 in elderly subjects [21] found increases in proportion of total, helper and activated T lymphocytes, and phagocytic cell activity. More studies have been conducted in younger adults where immunomodulating effects been reported for *L. casei* DN-114001, *B lactis BB12* and *L. plantarum*.

3. Inflammation

The inflammatory process plays a central role in the development and progression of numerous pathological situations, such as inflammatory bowel disease, autoimmune and neurodegenerative diseases, metabolic syndrome, and cardiovascular disorders, and low grade chronic inflammation

is a common feature of obesity, non-alcoholic fatty liver disease and ageing. Interestingly, probiotics can have both immune-stimulatory and anti-inflammatory activity, probably because they 'normalise' the immune response under conditions where homeostasis is affected such as in immunosenescence and obesity.

Certain probiotics have been demonstrated to exert systemic anti-inflammatory effects, e.g. decreasing the inflammation marker C-reactive protein (CRP) and pro-inflammatory cytokines such as TNF-alpha and IL-6, or increasing anti-inflammatory cytokines like IL-10. Custodero et al. [22] conducted a meta-analysis of probiotic studies that investigated CRP and IL-6 as markers of inflammation. They identified 5 studies that met the inclusion criteria with a total of 210 older subjects some with type 2 diabetes. Probiotics significantly reduced both markers of inflammation – the tested strains were the high dose mixture VSL#3, yogurt with *B. lactis* Bb12+ *L. acidophilus* La5 and capsules of *L. acidphilus*+ *L bulgaricus* + *L casei.*

It is important to consider whether the changes induced in immune system markers in the elderly translate into improvements in actual functional outcomes. A systematic review by Coutts al [23] found little evidence for benefits of probiotics or prebiotics on frailty, mortality, physical function, length of hospital stay. Nevertheless, a number of studies have indicated improvements in vaccine response and also in infections.

4. Vaccine response

The response to vaccination in older individuals is much less effective than in younger age groups. For example, the clinical effectiveness of influenza vaccination drops from 70–90% efficacy in young adults, to 17–53% in the elderly [24]. Lei et al. [25] conducted a systematic review and meta-analysis of randomized controlled trials (RCT) of the effectiveness of probiotics and prebiotics on the response to influenza vaccination. Based the results of 20 RCTs,14 of which were conducted in older (>65y) subjects, the authors concluded that pro and prebiotics improved seroprotection and seroconversion rates towards three influenza vaccines. The meta-analysis (based on 9 RCTs, 623 subjects, average age 74.8y) revealed seroprotection rates for influenza H1N1, H3N2 and B vaccines of 53%, 84% and 53% in those taking probiotics or prebiotics, compared with 37%, 67% and 50% in controls. Probiotics showing enhanced immune responses to influenza vaccination include *B. longum BB536, L. plantarum CECT7315/7316*, *L. fermentum CECT5716* and *B. lactis Bb12.* Prebiotics (FOS and GOS) showed less consistent effects.

5. Upper respiratory tract infections (URTI)

The improvements in markers of immune function induced by probiotic consumption, especially in older subjects with immunosenescence has the potential to reduce the incidence of respiratory tract infections, such as colds and influenza. A systematic review and meta-analysis by Hao et al. [26] of 12 RCTs mostly with children and adults of average 40y, found that probiotics significantly reduced the number of people experiencing episodes of acute URTI (odds ratio 0.53 $p < 0.001$) as well as the mean duration of an episode (–1.89 days $P < 0.001$) and the antibiotic prescription rate. A more recent systematic review [27] identified 8 RCT's investigating acute URTI in older subjects (>60 years). The probiotics used included *L.casei* DN-114001, *L casei* Shirota, *L. rhamnosus* GG and *Bacillus subtilis*. Overall the reviewers concluded that probiotics were better than placebo in influencing certain URTI outcomes, however the results were very variable, with not all strains being effective. In general, most strains (except *B. subtilis*) had no significant effects on incidence of infections, but some, notably *L casei DN-114001* (2/2 studies) and *L. casei* Shirota (1/2 studies) reduced the duration of episodes. In a study not included in the Strauss review [27], Shinkai et al. [28] reported that a heat killed preparation of *L. pentosus* b240 for 20 weeks reduced the incidence, but not duration, of common cold infections in older (>65 years) subjects.

The effects of probiotics on URTI raises the intriguing possibility of beneficial effects on Covid-19 infections, but this topic awaits investigations.

6. Digestive health

Disorders of the GI tract are reported to be the third most common reason for visits by older people (>65) to family doctors [29]. In the case of diarrhoea, the most common causes are infectious diarrhoea, diabetic diarrhoea, excessive use of laxatives or diuretics, and food-borne toxins. It is also a familiar complication of antibiotic use (antibiotic-

associated diarrhoea; AAD) especially in hospitals, nursing homes and chronic care facilities. The condition is particular serious in the 10–30% of cases where the pathogen *Clostridium difficile* is involved [30].

The impact of probiotics on AAD and *C difficile* infections has been extensively studied in both children and adults and has been the subject of numerous systematic reviews and meta-analyses. The most comprehensive of these, a Cochrane review by Goldenberg et al. [31] identified over 100 RCTs of which 39 met the inclusion criteria and 31 (8672 participants receiving antibiotic therapy) were included in the meta-analysis. The analysis revealed that probiotics reduced the risk of *C. difficile* associated diarrhoea (CDAD) from 4.0% in the placebo group to 1.5% in the probiotic group (RR 0.40, 95%CI 0.30–0.52) – a 60% reduction in risk. The results were similar whether considering adults vs children and impatient vs outpatients. The pooled analysis indicated a statistically significant decrease in the risk of AAD in adults (RR 0.60, 95% CI 0.49 to 0.72). Only four of the reviewed studies focussed on older subjects, three showed no significant effects, but one showed a markedly reduced risk of CDAD (RR 0.05).

Chronic constipation is a frequent gastrointestinal disorder and the prevalence increases with age: 16% of men and 26% of women 65 years and older declare themselves to be constipated [32]. There have been numerous RCTs of probiotics on functional constipation in patients and normal subjects, investigating effects on various endpoints including transit time, stool frequency and stool weight and consistency. There are at least 6 systematic reviews and/or meta-analyses, the latest of which [33] reviewed 21 RCTs (comprising 2656 subjects with constipation). Overall, probiotics (lactobacilli and bifidobacteria strains) were found to be moderately efficacious in increasing stool frequency (by 0.83 /week) and decreasing intestinal transit time (by approximately 15 hours) with no effects on stool weight, but the reviews detected significant heterogeneity in the data probably due to inter-species or inter-strain differences between probiotics. *B. lactis* strains including DN-173010 and HN109 were particularly beneficial. It should be noted, however, that there were few studies in older adults, with only one having digestive health as the primary endpoint [34]. This RCT showed no improvements in gastrointestinal symptoms after consumption of *L. reuteri* for 12 weeks. Overall, results of RCTs on probiotics in older subjects were inconclusive, with about half reporting beneficial effects, which in some cases may have been attributable to the inclusion of prebiotics in the supplements [35].

In contrast to probiotics, the effects of prebiotics on markers of digestive health are much more consistent. A systematic review and meta-analysis [36] of the effects of prebiotics on functional constipation concluded that prebiotics increased weekly stool frequency by 1 bowel movement and improved stool consistency. Indeed 3 prebiotics, lactulose, lactitol and chicory inulin, have received favourable opinions on health claims associated improving constipation symptoms from the European Food Safety Authority (EFSA). On the basis of 6 RCTs, the EFSA panel concluded that at a dose of 10 g/day, lactulose contributed to a reduction in intestinal transit time [37]. Similarly, 12 studies with 10 g lactitol/day demonstrated increased stool frequency, 5 of 6 studies showed improved stool consistency and 2 studies increased stool bulk [38]. Increased stool frequency was also reported in 6 studies with chicory inulin at 12 g/day [39].

7. Metabolic syndrome and type 2 diabetes

Metabolic syndrome (MetS) is a term that refers to subjects who have 3 or more of the following symptoms: abdominal obesity, glucose intolerance, insulin resistance, high triglycerides, low HDL-C, high blood pressure (>140/90mm Hg). It is estimated to affect 25% of adults in the UK.

Prospective cohort studies consistently suggest that yogurt consumption may contribute to a reduction in adiposity indexes and the risk of metabolic syndrome. A systematic review by Saez-Lara et al. [40] identified 14 RCTs of probiotic or probiotic+ prebiotic treatments conducted in subjects with MetS or Type 2 Diabetes (T2D). The majority of the studies showed some beneficial effects on various endpoints related to MetS and T2D. For example, RCTs in T2D patients with a mixture of *L. acidophilus* La5 and *B lactis* Bb12 resulted in significant reductions in fasting glucose, HbA1c, total and LDL-cholesterol and an increase in HDL-cholesterol. Improvements in plasma insulin, LDL-cholesterol, HDL cholesterol and triacylglycerols were also reported in T2D patients given a combination of *L. sporogenes* and the prebiotic inulin. The studies were conducted in young or middle adults and none used older subjects.

8. Blood lipids

Studies of the effects of probiotics on blood lipids have been mostly conducted in young or middle-aged adults, particularly in those with hypercholesterolaemia. A recent meta-analysis of RCTs of probiotics in hypercholesterolaemic adults [41] reported modest reductions in total cholesterol (–0.25 mmol/L) and LDL-cholesterol (–0.17 mmol/L, but no overall changes in HDL-cholesterol or triglycerides.

There are few studies of the influence of probiotics or prebiotics in older subjects. Constabile et al. [42] investigated the effects of a probiotic *L. rhamnosus* GG combined with a commercial soluble corn fibre on various parameters in 40 healthy older subjects (60–80 y). Amongst other findings, the combined probiotic+ prebiotic mixture reduced both total cholesterol and LDL-cholesterol in subjects that had elevated concentrations at baseline.

9. Cognition and dementia

As the average age of populations has increased, the incidence of dementia has also risen and is currently the fifth leading cause of death worldwide with Alzheimer's Disease (AD) accounting for up to 70% of cases [43]. The developing knowledge around the gut-brain axis, i.e. communication between the GI tract and the central nervous system via the vagus nerve, has led to interest in the potential of probiotics to affect cognition. Two studies in healthy elderly subjects with various strains of bifidobacteria showed minor effects on cognitive function tests (reviewed by Hutchinson et al. [35]). In a study with subjects having mild cognitive impairment, Hwang et al. [44] reported some improvement in performance of a battery of neurocognitive function tests after consumption of an *L plantarum* -fermented soybean preparation. However, a systematic review of probiotics (3 studies with strains of lactobacilli and bifidobacteria) in patients with AD, showed no beneficial effects on cognitive function [45].

10. Conclusions

The number of systematic reviews and meta-analyses of studies on probiotics and prebiotics attests to the wealth of evidence for health benefits. Studies in older people are fewer in number than those in younger age groups, but there is reasonable evidence for beneficial effects in the areas of immune function, upper respiratory tract infections and digestive health suggesting that probiotics and prebiotics may be useful dietary supplements to ameliorate some of the age-related disorders that are becoming increasingly common in our ageing society. There is a clear need for more trials in older subjects to identify the most effective strains and also to explore effects in areas such as metabolic syndrome and cognitive function to build on promising results in preliminary studies.

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Conflict of interest

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