Manipulating the microbiome of bacteria living in our guts could bring relief for sufferers of chronic diseases and allergies, and boost immunity. Discuss.

INTRODUCTION

Today, with the number of studies exploring the role of the gut microbiome in human health increasing exponentially (Huang et al., 2019), there has been a growing appreciation for how the gut microbiota potentially impacts human disease status. An interview with a gastroenterology professor illustrates that the impact of the gut microbiome on allergy, immunity and chronic disease is a topical research topic, and currently many researchers are planning to carry out further studies to confirm results. Many studies suggest the association between the gut microbiome and its impact on chronic disease and immune function, whilst evidence suggests that the imbalance of the gut microbiome can lead to metabolic disease (News-Medical, 2018). Comprehending the complexity of interactions between the factors contributing to the human gut microbiome, and the microflora colonising the human gastrointestinal tract, can help modulate the microbiome to help manage associated disease in a personalised way (Xu and Knight, 2014), and aid the restoration of a healthy, symbiotic microbial community. Currently, with chronic disease being estimated to kill almost 41 million people a year worldwide, making it seven out of ten deaths globally (O'Hare, 2020), and the opportunities for the manipulation of the gut microbiome to improve human health developing, extrapolating this to chronic disease, allergies and boosting immunity should be discussed.

CHRONIC DISEASE, ALLERGIES, IMMUNITY

Broadly defined as "conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both," (Centers for Disease Control and Prevention, 2020) chronic disease has the potential to worsen the overall quality of life of patients (Megari, 2013).

Chronic disease is generally caused by key risk behaviours, such as poor nutrition or tobacco use (www.cdc.gov, 2022), and usually by making healthier choices, quality of life increases and the development of chronic disease is reduced (Centers for Disease Control and Prevention, 2020). Allergies are the body's reactions to something that is usually harmless, for example, tree or grass pollen (NHS Choices, 2019), and today, allergies are the most common chronic disease in Europe (Allergy UK, 2022). Immunity refers to the body's ability to prevent invasion from pathogens (St-Amant et al., n.d.). A healthy immune system supports optimal living, from feeling healthy, to ensuring fewer infections, and prompting wounds to heal faster (Team, 2022).

THE GUT MICROBIOME

Comprised of trillions of microorganisms in the human gastrointestinal (GI) tract, the gut microbiota interacts with the host to control behavioural and biochemical processes from within the gut (Sciencedirect.com, 2011). From having a significant role in homeostasis, to the production of metabolites (Sciencedirect.com, 2011), the gut microbiome both directly and indirectly influences human health (Clemente et al., 2012). Various factors contribute to everyone's unique microbiome composition (Hasan and Yang, 2019) (Figure 1), intrinsic factors include genetics and microbials, whilst extrinsic factors like diet and antibiotics also have a role (Sciencedirect.com, 2011). The gut microbiota can be manipulated by altering the population and composition, or changing the functional metabolic activity of the microbiota (Lee et al., 2018). Dysbiosis of the gut microbiome has been linked to a variety of chronic diseases, such as obesity and cardiovascular disease (Lee et al., 2018). Achieving a healthy gut microbiome may have a positive impact on the treatment of these diseases, whilst regulating specific microbial groups can improve disease prevention and management (Lee et al., 2018). Thus, the modulation of the gut microbiome may have useful therapeutic and clinical applications (Lee et

al., 2018), hence the extent to which its manipulation could bring reliefs to sufferers of chronic disease, allergies and boost immunity should be considered.

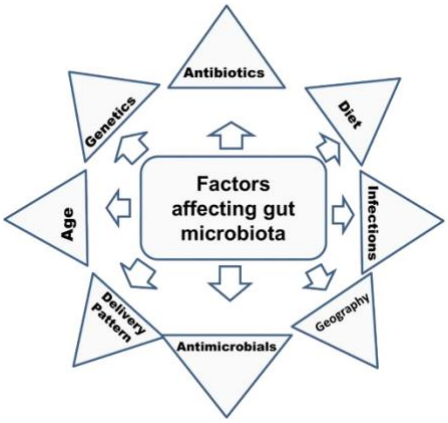

Figure 1: Factors affecting the human gut microbiome composition

(Madhogaria, Bhowmik and Kundu, 2022)

DISCUSSION

Clinical approaches to manipulating the gut microbiome usually focus on depleting excess microbes or the overall microbial load using antibiotics, antifungal agents, diet manipulating or by supplementing with live microbes (Durack and Lynch, 2018).

DIETARY INTERVENTION AND NUTRITIONAL SUPPORT

Various studies have shown that diet can alter the composition of the gut microbiome (Daliri et al., 2020), and evidence suggests eating a healthy diet can help cope with and manage the symptoms of chronic disease (Cleveland Clinic, 2016) (Better Health, 2012), and optimise immune function (CDC, 2022). Dietary intervention refers to “supplementing a specific ingredient, or a food from the diet, or excluding/restricting it, thereby modifying its intake,” (Guo et al., 2019).

Diets high in fiber levels can be used to help bring relief to sufferers of chronic disease, as it affects the type and amount of microbiota in the gut (Boston and Ma 02115 +1495-1000, 2017), and increases production of short chain fatty acid (SCFA) producers (Fu et al., 2019). SCFA's have a range of health benefits, from having cardiovascular protective properties to immunoregulatory characteristics (Xiong et al., 2022), thus increasing production can improve health. The complementary effects of increased dietary fiber consumption is supported by research evidence illustrating that the use of a Mediterranean diet, consisting of large amounts of dietary fiber (www.northernpaincentre.com.au, n.d.), rather than a typical Western diet, has been associated with a reduced risk of type 2 diabetes, heart disease, stroke and obesity (Harvard School of Public Health, 2018). Moreover, a study showed that feeding patients with type 2 diabetes a high fiber diet, promoted an abundance of SCFA producers, improved the metabolism of glucose (Zhao et al., 2018), regulated levels of blood sugar and improved insulin resistance (Brown, 2016). Furthermore, in terms of other chronic illnesses, higher levels of SCFA's were shown to improve the symptoms of ulcerative colitis and Crohn's disease, both of which are types of inflammatory bowel disease, and consist of chronic bowel inflammation (Brown, 2016). Furthermore, higher levels of SCFA's reduce the risk of heart disease by reducing inflammation and cholesterol levels (Brown, 2016). Thus, increasing fiber intake, resulting in increased SCFA's, could help bring relief and manage the effects of chronic disease, as chronic illness generally develops and is maintained in a vicious cycle (Harvard Health, 2021). This is as the most common chronic conditions are intrinsically related and are risk factors of each other, meaning a lack of control increases the likelihood of developing another (Harvard Health, 2021). Some of the most common, closely related chronic conditions include obesity, high blood pressure, type 2 diabetes, high cholesterol, and heart disease (Harvard Health, 2021). Thus, by using a high-fiber diet to manipulate the gut microbiome, which in turn increases the production of SCFA's, can help reduce the risk of developing other chronic conditions which consequently reduce the likelihood of comorbidities. This can specifically aid the ageing population with managing and controlling the effects of chronic disease, as they are the most common strata to develop chronic illness (Ansah and Chiu, 2023), and are more susceptible to developing multi-morbidities (NIHR, 2018).

However, recent interventional studies highlight that a significant increase in fiber consumption could temporarily reduce the diversity of the gut microbiome (Zhao et al., 2018). This is as the microbes that would digest fiber are modified, causing a change in composition, and through competitive interactions result in a reduction in microflora diversity (Zhao et al., 2018). Moreover, research suggests that an increased fiber intake alone over an extended period of time may not solely increase microbiome diversity (Weaver, 2021). This could be an issue in helping manage the effects of chronic disease for sufferers, as the main difference in the composition of the gut microbiome between healthy individuals and sufferers of chronic disease is a lower microbiome diversity (Vijay and Valdes, 2021), and being unable to restore symbiosis may therefore not contribute to relief. However, when a high fiber diet was coupled with the use of fermented foods, it resulted in health benefits such as aiding weight maintenance (Weaver, 2021). This is useful for sufferers of chronic disease as making lifestyle changes, such as losing weight, are important in chronic illness management and can aid quality of life and increase longevity (Harvard Health Publishing, 2017). This suggests that manipulation of the gut microbiome through multiple dietary methods can promote positive outcomes for sufferers of chronic disease.

Additionally, dietary intervention may require monitoring to ensure positive outcomes. This is as pesticides that may be found on food may impact the gut microbiome composition and may contribute to perturbations (Tu et al., 2020). This suggests that nutrition and dietary interventions to help relieve the impact of chronic disease may not always result in positive outcomes.

MICROBIAL SUPPLEMENTATION

Manipulating the gut microbiome can also be done using prebiotics, probiotics or bacteriophages for targeted effects (Lee et al., 2018) (Figure 2). Clinical and experimental research demonstrates that probiotic, prebiotic, and symbiotic supplements on the gut are beneficial, and may help the imbalance of the gut microbiota and reduce inflammation (Mafra

et al., 2019), thus suggesting that manipulating the gut microbiome in such ways may reduce the severity of some disease.

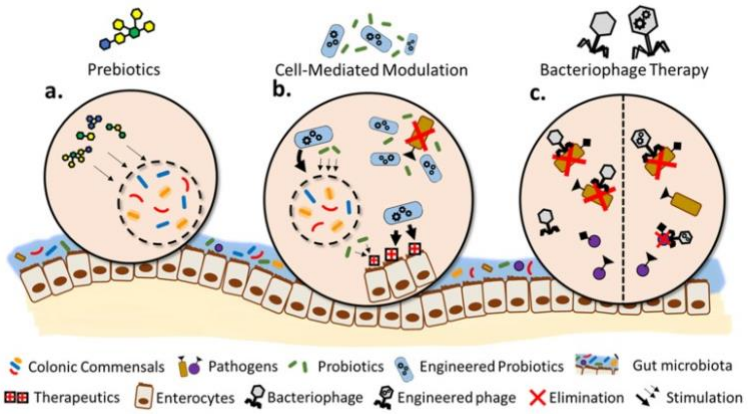

Figure 2: Targeted methods for manipulating the gut microbiome

(Lee et al., 2018)

a) How the use of prebiotics could aid the growth of useful microbes
b) How probiotics could change functional output
c) How the use of bacteriophages could target pathogens

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Scott et al., 2015). Probiotics could potentially alleviate the consequences of allergies (Lopez-Santamarina et al., 2021), whilst the use of probiotics and prebiotics together, have been useful in reducing asthma like symptoms and reducing the use of asthma medication (Lopez-Santamarina et al., 2021). Moreover, a separate follow up trial for children with peanut allergies found that 67% of children receiving probiotics remained desensitized 4 years following intervention compared to the 4% of the placebo group (Hsiao et al., 2017). This suggests that a combined intervention approach to food allergies has useful long-term efficacy, thus it could be useful in helping to relieve the effects of allergies on sufferers. However, the research limitations make it hard to know whether this would translate to better clinical outcomes, as there was no microbiome supplementation alone in a group, thus, whether this could alone have an impact on later outcomes or whether immunotherapy,

or both together had a key role is unknown (Durack and Lynch, 2018). This causes issues with identifying whether improved microbial supplementation itself, can help prompt positive outcomes and manage the effects of chronic disease, and allergies for sufferers, or whether microbial supplementation coupled with other interventions may provide a more valuable mean for relief of allergies.

Probiotics may also have positive effects on the treatment of some chronic brain disease, through the effect on the microbiome-gut-brain axis (Ansari et al., 2023) (Figure 3). The increasing number of probiotics in the colon can also have a therapeutic effect on mental disorders (Liu, Cao and Zhang, 2015) (Ansari et al., 2020). For example, restoring the gut microbiome in patients with Alzheimer's can slow down the progression of abnormal changes in the brain by reducing amylogenesis, and inflammation (Pluta et al., 2020). This suggests that the manipulation of the gut microbiota through the use of probiotics can help prevent the onset of more severe symptoms, thus improving the quality of life of sufferers, and relieving the effects of chronic disease.

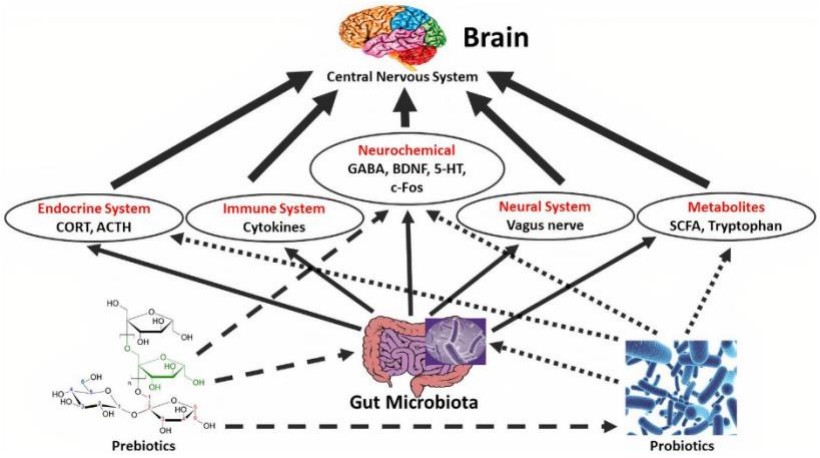

Figure 3: The role of prebiotics and probiotics on the central nervous system through the effect on the microbiome-gut-brain axis

(Ansari et al., 2023)

Furthermore, a systematic review (Hungin et al., 2018) showed that some probiotics were beneficial in reducing the overall symptom burden, and abdominal pain in specific gastrointestinal (GI) disorders (Guo et al., 2019). However, whilst the use of probiotics in this way may be beneficial, other means of manipulating the gut microbiome, such as, through fecal microbiota transplantation (FMT) strategies, show varied success for sufferers of irritable bowel syndrome and inflammatory bowel disease. This is as it was shown to be effective in 36% of patients, whilst 16% had mildly improved discomfort, and it was non-effective in the other 47% (Zhou et al., 2018) (Gearry et al., 2016). This suggests that manipulation through FMT strategies may not always improve the pain associated with chronic GI conditions, thus all manipulation of the gut microbiome may not be useful in always relieving the effects of chronic disease on sufferers.

Prebiotics refer to a "selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health" (Scott et al., 2015). Prebiotics are a non-pharmacological approach to aid the reestablishment of gut symbiosis, thus, promoting well-being (News-Medical, 2018), by stimulating the growth of useful gastrointestinal flora, and consequently preventing abnormal microorganisms developing (News-Medical, 2018). Prebiotics can resist the hydrolytic activity in the upper gastrointestinal tract thus reaching the colon intact, where they can change the composition of the gut microbiome, translating into strengthening the immune system (News-Medical, 2018). Prebiotics can help boost the immune system by improving pathogen resistance, this is by reducing the gut pH to limit the growth of some harmful microorganisms (Lab, 2020), such as *Clostridium difficile* (Boston and Ma 02115 +1495-1000, 2017), whilst strengthening the intestinal barrier lining against pathogenic microbes (Lab, 2020). Moreover, prebiotics aid the reduction of inflammation through increasing anti-inflammatory cytokine expression and reducing proinflammatory cytokine expression (Lab, 2020). This may help bring relief to sufferers of chronic disease as many chronic illnesses are supplemented by inflammation, and controlling the inflammation is part of the treatment, whilst uncontrolled inflammation can result in long-term health ailments (MD, 2022). Thus, prebiotics can

manipulate the gut microbiome to boost immunity and consequently bring relief to sufferers of chronic disease and help sufferers manage their condition.

Moreover, the use of pre-and probiotics is likely to positively influence the wider quality of life of sufferers of chronic disease. For example, a meta-analysis showed that probiotics could be useful in improving perceived sleep quality (Le Morvan de Sequeira et al., 2022). This is useful in helping manage the impact of chronic disease on sufferers, as the role of sleep health in the management of chronic disease has grown due to increased research suggesting insufficient sleep may aggravate the impact of chronic disease (CDC, 2019). Thus, manipulation of the gut microbiota through such interventions can improve the management of other consequences of chronic illness, namely, poor, insufficient sleep (CDC, 2019), thus lending support to the manipulation of the gut microbiome to help bring relief to sufferers of chronic disease.

Whilst interventional studies using microbial supplements show promising results, further research with high levels of control, greater attention to microbial strain based on functional characteristics, as well as the specific timing and duration of supplements could improve future studies (Durack and Lynch, 2018). This is as currently, research involves different patient populations, and varying probiotic formulations (National Institutes of Health, 2017), making it harder to determine whether microbial supplementation alone proves to be a useful method for relieving the impact of chronic illness.

CONCLUSION

Many of the research findings in principle suggest that the gut is a useful therapeutic target in helping bring relief to sufferers of chronic disease, allergies and to boost immunity. However, a larger number of placebo-controlled, randomised, double-blind studies using humans are required to confidently establish cause and effect, and to know whether intervention through manipulation of the gut microbiome can prompt positive clinical outcomes in real-world settings (Ansari et al., 2023). This is as there have been numerous non-human animal studies, whilst many trials make use of in vitro methods, thus making it inconclusive to establish

whether gut microbiome manipulation would provide a useful strategy against chronic disease in humans. Moreover, further research to respond to unanswered questions requires greater focus, for example, what a healthy gut microbiome actually looks like, and whether there could be any long-term implications of manipulating the gut microbiome. Despite this, nutrition coupled with microbial supplementation, using pharmabiotic methods, and individualised treatment, to manipulate the microbiome of bacteria living in the human gut, provides a promising outlook (De Gregori et al., 2016) as a method to help bring relief to sufferers of chronic diseases, allergies, and to boost immunity.

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