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Journal of Functional Foods 87 (2021) 104753

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Exploring the potential of prebiotic and polyphenol-based dietary interventions for the alleviation of cognitive and gastrointestinal perturbations associated with military specific stressors

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ARTICLE INFO

Keywords:
Polyphenols
Gut microbiota
Gut Microbiome
Prebiotics
Military personnel
Stress

ABSTRACT

Active military personnel are often subject to extreme stressors, whether psychological or physical. Such stressors often result in soldiers having severe gastrointestinal diseases and cognitive perturbations such as Post Traumatic Stress Disorder (PTSD). Whilst pharmaceutical treatments are available, they are not always the most viable option, either because of poor efficacy, side effects, availability or economic detriment. By exploring the potential of beneficial nutritional interventions, it may be possible to establish whether the increased intake of certain nutraceuticals (such as polyphenols and prebiotics) could improve psychological and gut health in combat soldiers, and reduce the effects that PTSD and related gastrointestinal issues have on health and well-being. This report investigates the link between prebiotics, polyphenols and cognitive and gastrointestinal health.

1. Introduction

The human intestinal commensal microbiota and its metabolic products are regarded as important contributors to host health (Cani, 2018). This mixed community of microorganisms, and its resulting functionality, contributes to complex biological processes within the mammalian system, and is instrumental in metabolic crosstalk which occurs between the host and microbiome (Burcelin, 2016; Qin & Wade, 2017).

There is a need to discover the cause of gut disorders and develop effective new therapies. This has resulted in a drive to expand research into treatment to proactively address issues and control symptoms. Although there is a stark lack of mechanistic evidence and only a small amount of clinical data, there is accumulating evidence that gut dysbiosis may be involved in the pathogenesis of many digestive disorders (Wang et al., 2017).

Although it is recognised that diet is one of the most modifiable indicators of human health (Leeming et al., 2019), the human gut microbiome is still fairly under-explored as an ecosystem (Arumugam et al., 2011; Kho & Lal, 2018; Vrancken et al., 2019). This is despite it providing an extraordinary opportunity to reduce the impact of common gastrointestinal diseases such as Irritable Bowel Syndrome (IBS) and gastroenteritis (El-Salhy et al., 2019), via dietary intervention to modify bacterial communities (Staudacher et al., 2017).

Recent research shows that there is potential for the use of gut mediated therapies to treat or at least control symptoms of psychological disorders, such as PTSD (Bersani et al., 2020; Leclercq et al., 2016). The ability of the gut microbiota to influence the biological state of an individual has led to an acknowledgement that research into the microbiome is an essential part of current and future healthcare strategies (Hadrich, 2018).

Not only is diet one of the most important modifying factors of the gut microbiota, but it is also instrumental in regulating stress related responses (Shively et al., 2020). This is because diet has an impact on the microbiota-gut-brain axis, especially in situations perpetuated by homeostatic challenge (Foster et al., 2017).

Routes of communication between the microbiota and brain are of growing interest and, whilst more information is needed, key components have now been identified: the vagus nerve; gut hormone signaling; the immune system; tryptophan metabolism; and microbial metabolites such as short chain fatty acids (SCFA) (Carabotti et al., 2015). Although it may initially seem incongruous that the gut can influence the brain, common phrases in most languages such as gut wrenching, gut feeling – even butterflies in the stomach - suggest an intuitive understanding of such a link between these organs.

Grasping the importance of the gut microbiome in both neurological

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https://doi.org/10.1016/j.jff.2021.104753
Received 12 April 2021; Received in revised form 9 September 2021; Accepted 11 September 2021
Available online 16 September 2021

and gastrointestinal pathologies and developing treatments is a major challenge for 21st century medicine. Nowhere is that need greater than in the military. Gastrointestinal illness is an extremely common reason for sick visits within military personnel (Riddle et al., 2015) and PTSD is present in (71%) of veterans (Armenta et al., 2018). These issues not only affect active duty performance but cause detriment to the economy of the military, and clearly damage the general well-being of soldiers.

By studying nutritional interventions such as pro- and prebiotics it could be possible, through exploitation of gut microbial communities, to develop safe and effective interventions. If this positively influences both gut health and the mental state of individual war fighters, it could mitigate many military-specific issues that are currently compounded by military-relevant physical, physiological and psychological stressors. Although a lot of research has been carried out on non-war fighter gut and brain health and their interactions, the role of the gut microbiota (and how it is affected by stress) is under explored.

This paper will focus on polyphenols and prebiotics; outlining their mechanisms of effect, identifying any crosstalk between different combinations and applying this to warfighter-specific problems. It will examine the potential for novel nutritional mixes (of prebiotics and polyphenols) to directly affect specific bacteria in order to attenuate or prevent gut dysbiosis and associated cognitive perturbations during stress exposure. By looking at interactive mechanisms, it may also be possible to discover whether or not current military MREs (meals ready to eat) could have effects on the potential benefits of prebiotics and polyphenols added to the military diet. By expanding knowledge on this subject and improving understanding of combinatorial nutritional supplementation, it may be possible to establish whether or not it is appropriate to treat certain warfighter associated physical and cognitive conditions through gut microbiota targeted dietary interventions. By examining both gastroenteritis and the neurobiology of cognition, the findings of this paper will be relevant to not only warfighter specific cases but also general health and wellbeing.

2. Military specific stressors

One primary reason to focus on war fighters is because they are in highly stressful situations. This paper will attempt to evaluate the potential for polyphenols and prebiotics to mediate stress response, whether cognitive or physical. It is important to note that, as there is a lack of warfighter specific research, civilian and (where available) athlete research will be used. Athletes may be a good representatives for war fighters as stressors commonly occurring in those groups are similar, i.e. strenuous exercise leading to injuries.

For the purpose of this study, stress is defined as ‘a disruption in homeostasis due to environmental, physical, or psychological stimuli (i.e., stressors) that elicits adaptive physiological and behavioural responses to restore homeostasis (i.e., the stress response)’ (Glaser & Kiecolt-Glaser, 2005). Although, as mentioned, this paper will categorise research on non-military personnel, it is still possible to examine stressors unique to the military situation. As such, stressors can be separated into physical (strenuous exercise, undernutrition, etc.), psychological (anxiety and consequent cognitive demands, etc.) and environmental (pathogens, high altitude, etc.) (Weeks et al., 2010).

Research has correlated these stressors with detriments to health such as nutrient insufficiencies, hormone disruption, injury or impairments (musculoskeletal and cognitive), inflammation and immune suppression, as well as general illness and infection (Karl et al., 2018).

Despite the belief that people can build tolerance, or resilience to stress (Dienstbier, 1989), it has been established that highly stressful situations can affect performance, cognitive abilities, illness and recovery time (Wu et al., 2013). It is, therefore, both interesting and reassuring that growing evidence has linked many stress related health conditions to dysbiosis of the gut, as it might prove to be the case that, by manipulating the gut microbiota through nutrition, we may mediate such responses in military personnel.

3. Gut-brain axis

Though a link between the gut microbiota and the brain has long been suspected, it is only in recent years that we have seen evidence of causal links between changes in the gut microbiota and brain function and behaviour. *In vitro* research has also revealed the potential molecular mechanisms involved in communication between the gut and the brain – the gut-brain axis, as illustrated in Fig. 1.

Interactions between peripheral intestinal function and cognitive and emotional centres of the brain appear to be bidirectional (Sun et al., 2020), and much research shows that communication is highly associated with signaling from the gut microbiota (Carabotti et al., 2015). Communication within both the central and enteric nervous systems (signaling from the gut microbiota to the brain and from the brain to the gut microbiota) involves endocrine, immune and neural mechanisms (Carabotti et al., 2015; Ma et al., 2019). Though much recent research has been in animal models (Park et al., 2013), links between the microbiota and the gut-brain axis have been demonstrated by correlations between gastrointestinal disorders such as IBS (Mayer, 2011), and cognitive disorders like anxiety or depression (Zheng et al., 2016).

Research has shown that the brain can affect the structure and function of the gut microbiota through modulation of gut motility and gut permeability. It has also been shown that through this bidirectional mechanism, direct secretion of hormones may directly affect microbial gene expression (Martin, Osadchiy, Kalani, & Mayer, 2018). These interactions are thought to be a circular communications loop and any disturbance within the loop can result in dysregulation. One example of this is where secretion of hormones such as 5-HT from enterochromaffin cells is seen to travel towards the gut lumen, potentially resulting In microbial alterations (Lund et al., 2018). This is likely a bidirectional relationship, where secondary bile acids and short chain fatty acids derived from the gut bacteria are responsible for the regulation of enterochromaffin cell derived 5-HT synthesis (Mandić et al., 2019).

Hormones can affect microbial gene expression in other ways, such as in the case of the increased virulence of pseudomonas aeruginosa, by norepinephrine (Hegde et al., 2009). Though the mechanisms of this are not fully understood, it is thought that the direct affectation of norepinephrine on the virulence of bacteria is through enhancement of bacterial attachment to host tissue (Freestone, 2013).

Not only is IBS associated with general detriment to cognitive function, but research has directly linked the hyper-arousal and hypervigilant state of PTSD to IBS as a result of the bidirectional signalling of the GBA (gut-brain axis) (Ng et al., 2019). Traditional diagnoses of PTSD rely on examination of behavioural symptoms (Spoont et al., 2010) but more recent evidence (as mentioned) has shown PTSD to be linked with immune system and inflammatory changes. IBS has been independently associated with PTSD (Iorio et al., 2014). A study showed that 36% of patients with IBS met behavioural and psychological criteria for diagnosis of PTSD (Irwin et al., 1996). It has also been reported that, specifically in female veterans, there was an increase of IBS in those diagnosed with PTSD (Savas et al., 2009).

Psychiatric illness is highly debilitating to some and often one of the most dangerous aspects is the risk of relapse. By taking a more holistic approach to the treatment of cognitive perturbations, such as exploring the potential for modulation of the gut microbiota to treat or lessen these, recovery may be improved.

Associations have also been made between microbiota and stress-related changes in behaviour and brain function. For example, one study explored whether postnatal microbial colonisation affected neuroplasticity and biological systems response. By using germ-free, specific pathogen-free and gnotobiotic mice, this study explored the hypothalamic–pituitary–adrenal (HPA) reaction to stress. It found that germ free mice had a substantially higher hypothalamic-pituitary axis response to stress, and that this exaggerated response could be reversed through colonisation by a probiotic *Bifidobacterium infantis* (Sudo et al., 2004). This suggests that commensal microbiota can strongly affect the

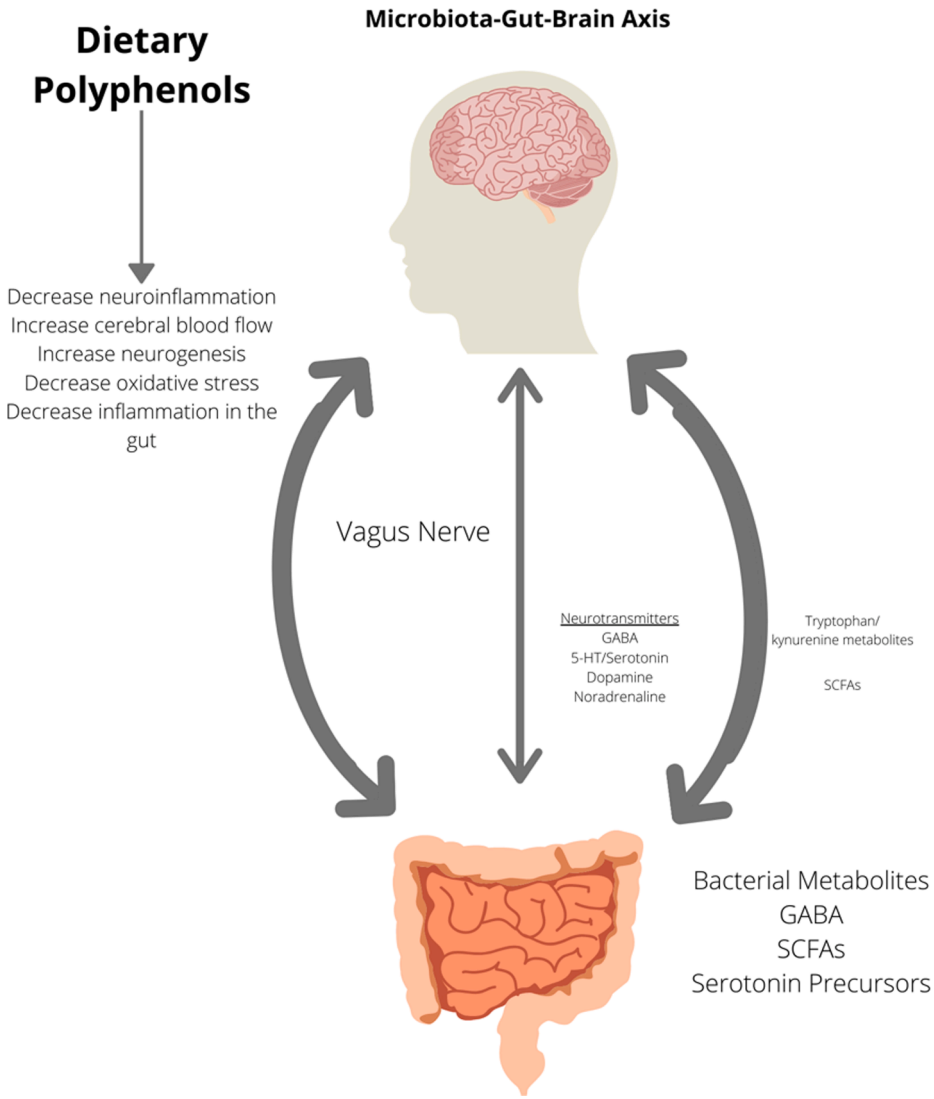

Fig. 1. Illustration of the gut-brain axis in the human superorganism. The putative effects of dietary polyphenols and the bidirectional communication of the microbiota-gut-brain axis are indicated. GABA: gamma-Aminobutyric acid; SCFA: Short Chain Fatty Acid; 5-HT, 5-hydroxytryptamine.

development of the stress response, that changes are not permanent and that the introduction of specific bacteria can alter the stress response. Though the idea of psychobiotics has been around since 2013 (Dinan et al., 2013), the use of bacterial and nutritional interventions has not been greatly explored in human studies. When it has been tested on humans it has often been on healthy human volunteers rather than exploring psychobiotics as a treatment for those in a disease state.

By looking at inflammatory biomarkers and hormonal levels associated with disease states, researchers have been able to associate dysregulation of immune function and the HPA axis with an individual response to stress and therefore, likelihood to develop PTSD (Neigh & Ali, 2016).

PTSD is often characterised by high pro-inflammatory cytokines and low cortisol responses (Gill et al., 2008; Kim, Yoon, et al., 2020; Kim, Lee, et al., 2020; Speer et al., 2018, 2019). Analyses have primarily shown increases in levels of pro-inflammatory cytokine interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ (Kim, Yoon, et al., 2020; Kim, Lee, et al., 2020). Research has shown that dysbiosis of the gut may increase susceptibility to PTSD after traumatic or high stress events (Leclercq et al., 2016). Furthermore, when stress alters the microbiota early in life, it can shape immune homeostasis and nervous system for the host (Borre et al., 2014), and increase the risk of developing PTSD later in life (Leclercq et al., 2016). It may therefore be possible, by targeting this dysbiosis, to manipulate the gut-brain axis with nutritional intervention or supplementation in order to reduce the likelihood of the occurrence of PTSD.

Research in mouse models, using intruder stressors, has shown that Firmicutes and Bacteroidetes are vulnerable to stress that can cause PTSD, and the ratio between these increases with increasing stress (Gautam et al., 2018).

By studying such links and how alterations affect different parts of this system, it may be possible to identify novel therapeutic targets to address cognitive disorders that have so far been poorly understood. Case study research has suggested that treatment of PTSD symptoms may alleviate symptoms of gastrointestinal illnesses, like IBS (Weaver et al., 1998).

There is a link between dysbiosis of the gut and cognition, as illustrated in a study that involved antibiotic disruption of colonic bacteria in adult mice (Fröhlich et al., 2016). The study found that, by treating these mice with antibiotics, significant changes occurred in metabolite levels, changing expression of certain molecules and hindering specific brain functions such as memory. It is posited that cognitive impairment correlating with dysbiosis, is related to HPA axis activity and changes in the expression of certain tight junction proteins (Fröhlich et al., 2016). This direct correlation of dysbiosis to cognitive impairments and biochemical alterations is relevant to PTSD.

Cirrhosis in veterans can be directly linked to PTSD with changes in the gut-liver-brain axis being observed. Studies have shown a lower microbial diversity in PTSD, with higher levels of pathogenic bacteria. Studies have correlated the increase of some pathobionts such as *Enterococcus* spp. with general poor cognition and have specifically linked *Shigella* spp. with PTSD patients (Bajaj et al., 2019). Interestingly, when combat-exposed veterans with PTSD were directly compared to combat-exposed patients with no PTSD, functionality was seen to differ in the gut-brain axis between the groups, demonstrating that PTSD was directly linked to differences in microbial diversity (Bajaj et al., 2019).

Of further relevance to military personnel is their diet, as an inadequate diet has been shown to have a deleterious impact on cognitive performance (Gómez-Pinilla, 2008; Lu et al., 2016). In a study during which young people were put into a military training environment with multiple stressors, increased intestinal permeability was exhibited as a response to the stress, and concentrations of microbial metabolites

in faecal samples were also altered (such as p-cresol which increased, and benzoate metabolites which decreased), with decreases in Bacteroidetes and increases in Firmicutes also being observed (Karl et al., 2017).

4. The gut microbiota

The human gut microbiome, comprised of various organisms such as bacteria, viruses, parasites and other microbes, has an enormous effect on health and disease outcomes (Clemente et al., 2012). This can be as a result of contributions to metabolic function which enhance resistance to disease by both improving immunity and protecting against pathogens. Through this metabolic action, the gut microbiome affects many human physiological functions. The majority of gut microbes are beneficial (or harmless) but dysbiosis is associated with diseases such as Inflammatory Bowel Disease (IBD) Irritable Bowel Syndrome (IBS), psychological/neurological disorders, certain cancers and obesity (Zhang et al., 2015). Dysbiosis can be defined as any change to the composition of resident commensal communities relative to the community found in healthy individuals (Petersen & Round, 2014). This discovery has improved understanding of how the microbiota may be modulated as a response to human health and has shown that the gut microbial community should be considered as a whole, rather than focussing on individual bacteria (Thursby & Juge, 2017).

Because gut microbiome profiles vary from individual to individual, specific characteristics of a healthy gut microbiome cannot be narrowly defined (Bäckhed et al., 2012; Conlon & Bird, 2014; Human Microbiome Project, 2012). Over 1000 phylotypes exist in the human gut but most of these belong to a few phyla: Bacteroidetes and Firmicutes are predominant, with other more minor constituents also commonly present (Rinninella et al., 2019). Examples of healthy adult microbiota have some gut bacterial species in common and, through culture-based studies, this has come to be considered as a 'core microbiota' (Guinane & Cotter, 2013; Ursell et al., 2012). However sequencing research has demonstrated that microbiota are highly temporally and spatially variable in the colon, which calls into question the validity of the idea of a 'core' microbiota (Parfrey & Knight, 2012; Ursell et al., 2012). Although the idea of this 'core' microbiota may no longer be universally accepted, a review paper has suggested that, alternatively, a core *microbiome* is shared by healthy gastrointestinal tracts (Lozupone et al., 2012). Though the terms are often used interchangeably, usually, microbiota refers to the actual bacteria, whereas the term microbiome often is used in a more functional capacity, describing the bacteria and their genes. The gut microbiome may be functionally highly similar, whilst hosting many different microbiota species due to varying environmental influences.

It is important that we understand effects that such environmental variations have on human health, as this may account for individuals' differing responses to drugs or dietary components. Host-specific responses to certain foods may involve pathways outside common functional metabolism (i.e. differential microbial metabolism). This is illustrated by a study which focused on the potential health benefits of consuming soy products. Many health benefits associated with soy consumption have been shown to be associated with the bacterial metabolism of soy isoflavone daidzein to S-(-) equol (Mayo et al., 2019). However, production of this beneficial compound seems to be reliant on habitual consumption of soy as shown by Rowland et al. (2000). This was further demonstrated by a comparison of studies on equol production in western countries versus those in Japan, Korea or China where soy was consumed as part of a habitual diet. It was shown that, while a non-western diet had a 50–60% occurrence of S-(-)equol upon dietary soy intake, the adult population of western countries produced only around 25–30% (Miura et al., 2016). This is interesting, not only because it demonstrates ways in which habitual diet can affect the processing of food components, but also because it has potential ramifications in medicine as key microbiota differences may affect drug metabolism in different populations.

Having established that habitual diet affects how dietary components are metabolised, it is also important to understand and explore resilience of the gut microbiota – in short – how much can the response to certain functional foods be changed by diet, for how long and how quickly? This is important when considering therapeutic diets such as introducing prebiotics, probiotics or polyphenol compounds. Human studies have usually demonstrated statistically significant changes to the microbiome when diet is changed over a period of time, for example, differences have been seen after 10 days of a high fibre diet (Wu et al., 2011). However, it is important to note that some changes in microbiome composition in one study were actually detectable within 24 h of controlling the diet (Wu et al., 2011). This was further confirmed in studies on gnotobiotic mice which demonstrated that switching from a low fat, plant polysaccharide rich diet to a high fat, high sugar western diet caused structural changes in the microbiota within a day. Not only was structure altered, but also gene expression and metabolic pathways in the microbiome (Turnbaugh et al., 2009). It is important however to note that, although these changes are observed and may have effects on potential health benefits conferred by eating certain foods (as in the case of soy), differences are still minimal compared to simple interpersonal variation.

The gut microbiota affects digestion and host nutrition by breaking down non-digestible substrates. This symbiotic relationship provides strong evidence of the importance of the gut microbiota for host health (Makki et al., 2018). One way that digestion of substrates contributes to host health is by releasing short chain fatty acids (SCFA) from indigestible fibres. SCFA may help modulate both the immune response and tumorigenesis in the gut (Bishehsari et al., 2018; Chambers et al., 2018).

The abundance of many bacteria may be inversely correlated to several disease states (Arboleya et al., 2016; Heiman and Greenway, 2016). It may therefore be possible to utilise dietary components to selectively enhance the growth of beneficial bacteria that improve host health (Zhang et al., 2015). While there is considerable research on the use of probiotics to improve gut microbiome health, prebiotics can also be used to maintain and improve health through nutritional interventions that increase the activity of bacterial groups such as *Bifidobacterium* and *Lactobacillus* spp. (Singh et al., 2017).

5. Pro, Pre, synbiotics and polyphenols – A brief introduction

The inclusion of probiotics, prebiotics or synbiotics into the human diet can favourably alter the intestinal microbiota. According to the latest definition by the International Scientific Association for Probiotics and Prebiotics, (ISAPP) probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill et al., 2014). Probiotics have been shown in clinical studies to have a positive effect on gastrointestinal diseases (Allen et al., 2004; Dale et al., 2019; McFarland, 2006) as well as disorders such as diabetes (Tao et al., 2020). Research has also shown that probiotics can aid the body's

immunity (Vanderpool et al., 2008) and be used prophylactically to attempt to prevent certain cancers (Kim & Jin, 2001; Lidbeck et al., 1991).

A prebiotic is defined by ISAPP as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson et al., 2017). Prebiotics stimulate the growth of different gut bacteria and can have a large effect on the modulation of the gut microbiota (Chung et al., 2016). Health benefits conferred from the intake of prebiotics can vary, but research has shown that prebiotics can aid in metabolic health (Kellow et al., 2014), allergic health (Brosseau et al., 2019), and gastrointestinal health (Lindsay et al., 2006; Welters et al., 2002). Prebiotics are found in fruit, vegetables, fermented foods, and can also be ingested through supplementation, as can probiotics (Markowiak & Śliżewska, 2017).

The term synbiotic was first introduced by Gibson and Roberfroid (Gibson & Roberfroid, 1995), and was described as a combination of synergistic probiotics and prebiotics, but in 2019 the definition was updated to " a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host" (Swanson et al., 2020). Synbiotics aim to aid the survival of probiotics in the gastrointestinal tract thereby, theoretically, improving their efficacy (Peña, 2007).

Plant polyphenols are compounds that may also meet the criteria of prebiotics (Gibson et al., 2017) and, whilst more evidence is needed, the health benefits linked to polyphenol consumption are associated with metabolites produced after microbial metabolism (Dueñas et al., 2015). Polyphenols are a large group of phytochemicals, with enormous variation in both structure, function and metabolite production (Tsao, 2010).

6. Prebiotics

The primary bacteria 'targeted' by prebiotics are *Bifidobacterium* and *Lactobacillus*, as these have evidence of health promoting effects (Manning & Gibson, 2004). Established prebiotics (through *in vivo* studies) include inulin, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), although there are other compounds that also meet the criteria of this definition (Davani-Davari et al., 2019). These are other oligosaccharides, algae, resistant starches, and polyphenols, which may positively affect bacteria within the gastrointestinal environment although there is less *in vivo* evidence than for fructans or galactans (Gibson et al., 2017)

By selectively modifying the gut microbiota through prebiotics, we may not only induce beneficial effects in the colon and surrounding digestive tract, but also potentially benefit other areas of the body. Research has shown that the prebiotic effect is associated with improvements in the activities of the immune system, and biomarker levels such as blood lipids (Markowiak & Śliżewska, 2017).

7. Mechanism of prebiotic action:

One of the primary mechanisms by which dietary fibre and other prebiotics change the gut microbiota is through fermentation in the colon (Slavin, 2013). The majority of bacteria in the human body are in the large intestine and this is the most diverse and metabolically productive area of the body (Louis et al., 2016). Due to a slow transit time, anaerobic conditions, favourable pH and readily available nutrients, bacterial growth is extensive therein. Bacteria that are potentially beneficial are often those with a solely saccharolytic metabolism, such as the lactobacilli and bifidobacteria mentioned previously (Ouwehand et al., 2005). The primary fermentation pathway generates pyruvate from hexoses in undigested carbohydrates (Oliphant & Allen-Vercoe, 2019). Then, colonic bacteria hydrolyse many of these to produce CO2, SCFA and other compounds, some generating energy from the fermentation (Slavin, 2013). SCFAs can be absorbed into the bloodstream and some, like acetate, are metabolised systematically (Hernández, Canfora, Jocken, & Blaak, 2019). The production of SCFAs through fermentation in the colon is also thought to repress pathogen growth by reducing the intestinal pH (den Besten et al., 2013). One positive aspect of the introduction of prebiotics to improve host health is that prebiotics occur naturally in many foods, such as garlic, onions, soybeans, wheat, banana, asparagus, artichoke and oats (Slavin, 2013).

Although fibre and thereby, some prebiotics, are recommended in nutritional guidance, their intake is small in western diets (Holscher, 2017). It may be possible however, to confer health benefits to those unable to consume the necessary amounts by nutritional interventions such as fortification of foods with prebiotics. If we consider polyphenols to have a prebiotic effect, highly concentrated derivatives of plants containing these, as well as other prebiotic supplements, could be added to foodstuffs.

One often overlooked group of people unlikely to consume enough prebiotics (to counteract the harmful effects of physical and mental stress) is combat soldiers. Military personnel have to operate under conditions that civilians would not usually be subjected to, for example: poor sleep; less than ideal nutrition; extreme environments e.g. altitude, all of which can lead to elevated stress (Hill et al., 2011; Karl et al., 2018). Due to the nature of their job, combat soldiers are often required to perform their roles despite these suboptimal conditions, which has the potential to lead to poor health outcomes including cognition. 39% of military personnel report feeling a great deal of stress in their work and it is possible that these stressors and associated issues could dictate mission success or failure (Bray et al., 2001). It is therefore within the best interests of the military to ensure that everything possible is done to ensure optimum cognitive and physical performance of military personnel. Studies have demonstrated that, although the gut microbiome does generally display some stability, it is possible for stressors to alter gut microbiome composition (Karl et al., 2018). Gut microbiota could, therefore, be manipulated to modulate the human stress response to improve host health, and growing evidence does show that a healthy gut microbiota has positive effects on military performance (Arcidiacono et al., 2018).

Not only could acute stress hamper performance (Bray et al., 2001) but continued and chronic stress and trauma experienced by some military personnel may result in cognitive perturbations such as PTSD (Iribarren et al., 2005). The prevalence of PTSD in military personnel may be twice as high as in civilian populations (Spottswood et al., 2017).

The gut microbiome is known to have a critical role within the brain-gut axis, and in regulation of intestinal permeability, (Carabotti et al., 2015; Kelly et al., 2015), so nutritional supplementation to improve function of the gut microbiome may be fundamental when considering the treatment and prevention of PTSD. Because of its association with low grade inflammation, PTSD may result in deficits in intestinal permeability (Bersani et al., 2020; Kim, Yoon, et al., 2020; Kim, Lee, et al., 2020; Leclercq et al., 2016). Therefore, it is feasible that treatment (curative and proactive) through manipulation of the gut bacteria by nutritional intervention, could benefit military personnel. It is also important to note that, while a diet of USA military food rations alters faecal microbial composition, it does not directly increase intestinal permeability (Karl et al., 2019).

It has been postulated that prebiotics provide a protective effect on cognition through aiding of production of Brain-derived neurotrophic factor (BDNF) (Burokas et al., 2017; Franco-Robles & López, 2016). This is particularly relevant to those in high stress situations, as BDNF has been shown to decrease when acute stress occurs. In brief, supplementation with prebiotics such as inulin, will possibly modulate the gut-brain axis, by increasing BDNF levels and reducing pro inflammatory cytokine concentration. One study (Romo-Araiza et al., 2018) using a mouse model suggests that the prebiotics increase the effects of beneficial bacteria, or probiotics, thus increasing butyrate production, which results in these positive changes. By increasing the intake of prebiotics, and therefore promoting an increase in the microbial diversity, cognition may be protected. A study has further supported the association

between prebiotics and BDNF by supplementing rats with a prebiotic, showing that the levels of BDNF were elevated in the prebiotic group, compared to a control (Williams et al., 2016).

Although probiotic supplements have been studied in relation to improving individual performance (Agans et al., 2020), the use of prebiotics is relatively under explored in this population. Research has shown that prebiotic supplementation can alter cognitive states in some individuals, including increased attention to positive emotional cues and improved mood (Schmidt et al., 2015). Other studies have shown that consumption of inulin resulted in better accuracy in recognition memory tasks, and improved recall performance (Smith et al., 2015).

8. Polyphenols

Polyphenols are ubiquitous plant chemicals. They are structurally categorised by the presence of large multiples of phenol structural units and have, in recent years, become a focus of nutritional research. Due to their abundance in plants, they naturally form a part of the human diet and evidence suggests that consumption of these molecules is a key modulator of human health. Though previously thought to be due to direct antioxidant effects, beneficial modulation of both physical and cognitive health by polyphenols is now widely accepted to be due to interactions with the gut microbiota, with metabolites of these interactions providing beneficial effects throughout the host system (Kennedy, 2014).

There are over 8000 types of polyphenol (currently identified) but they are broadly categorised (as a function of the number of phenol rings that they contain and on the basis of structural elements that bind these rings to one another) into flavonoids (which account for roughly 60% of all polyphenols), phenolic acids, stilbenes and lignans (Pandey & Rizvi, 2009; Tsao, 2010).

Polyphenols can be generally divided into two main groups – Flavonoids and non-flavonoids. The flavonoids are split into six groups: flavonols, flavones, flavanols, flavanones, isoflavones, and anthocyanins (Abbas et al., 2017), and non-flavonoids include stilbenes, lignans and phenolic acids (Pandey & Rizvi, 2009).

Polyphenols may initially be absorbed in the small intestine, often, though not always, conjugated with sugars or organic acids (although this usually only occurs with those structures that are mono or dimeric (D'Archivio et al., 2010)). This releases aglycones which enter the intestinal cell lining and undergo biotransformation, after which metabolic products are spread round the body or excreted (D'Archivio et al., 2010). Other, more complex structures will reach the colon intact, and can be metabolised therein by the gut microbiota. This transformation is mediated by microbial enzymes, and may include demethylation and decarboxylation, amongst other processes (Chen et al., 2018). It is important that we understand biotransformations mediated by phase I and II reactions in polyphenols, as it is these phases of metabolism that cause low bioavailability (in contrast with high bioactivity) (Luca et al., 2020). Poor absorption of dietary polyphenols results in extensive metabolism within enterocytes and the liver by phase I and II enzymatic reactions, followed by biotransformation by the gut microbiota into varying structures that can be circulated in the blood (Luca et al., 2020). One study estimated that less than 5% of dietary polyphenol intake is absorbed and reaches plasma unchanged (Faria et al., 2014). As mentioned above, low bioavailability/high bioactivity paradox means that metabolites, whether through enzymatic transformation or microbial degradation, are of great interest to the scientific community as they demonstrate significant mechanistic effects (Luca et al., 2020).

Known to be secondary metabolites in plants, dietary polyphenols are primarily involved in defence against oxidative damage (ultraviolet radiation) or damage caused by pathogen aggression. In humans, these protective effects seem to be transferred, and long-term consumption of diets high in plant polyphenols may protect the human superorganism against: cancer development and progression (green tea) (Yuan et al., 2018); cardiovascular disease (Khurana et al., 2013); neurodegenerative diseases (Mandel & Youdim, 2004)), and other chronic diseases (Jelena et al., 2018; Pandey & Rizvi, 2009). Polyphenol consumption has also been associated with modulation of human health through anti-inflammatory properties (Zhang & Tsao, 2016). There is much evidence that supports associations between the consumption of polyphenols and a reduced risk of chronic disease, and many reviews and research have stated that although specific classes of compounds are yet to be quantified and explored sufficiently to give specific recommendations, a diet high in polyphenol containing foods should be encouraged (Del Bo et al., 2019; Knekt et al., 2002).

One of the reasons that it is difficult to establish specific recommendations when exploring the protective effects of polyphenols is large methodological variation when collecting data (Del Bo et al., 2019). Furthermore, many intervention studies see a much higher dose of polyphenol content being administered than is realistic for a human to consume in a 'normal' healthy diet. (Williamson, 2017). There may also be different mechanistic actions of polyphenol isolates versus wholefood consumption – we see in broccoli, for example, that supplementation does not have the same beneficial effects as consumption of the whole food (thought to be due to a lack of the enzyme Myrosinase in supplements (Clarke et al., 2011; Gautam et al., 2018), so this should also be taken into consideration. Another difficulty when evaluating the efficacy of polyphenols in protecting human health is their myriad structures, each of which has a different metabolic pathway and physiological roles, which means that each individual compound's health effects should be explored – both long and short term (Carbonell-Capella et al., 2014). Whilst it is reasonable to recommend polyphenol intake, guidelines for supplementation need to be established.

One benefit of polyphenols is that they are often found in foods already associated with a healthy diet. Whole plant foods, such as fruits and vegetables, are high in polyphenols and the consumption of these foods is known to be safe and beneficial. Some specific foods that are high in polyphenols include green tea, cocoa, blueberry and cranberry, coffee, cereals, as well as nuts, seeds and vegetables such as artichoke (Pérez-Jiménez et al., 2010). We should note that, because deficiencies in polyphenol intake do not result in deficiency diseases (except in the case of general malnourishment), it is difficult to define appropriate reference intake values for such food components (Fraga et al., 2019).

Though many plant foods contain polyphenols, this paper will primarily focus on those that exist in tea, cocoa and berries (blueberry and cranberry). Before ndiscussing these specific foods, however, it is important to consider the types of polyphenol structures and differential bacterial metabolism. Considering the differing structures is important as variations will cause differences in physicochemical factors, such as digestibility. In order to assess bioavailability and metabolic influence of polyphenolic compounds, one must first, therefore, explore bioaccessibitfuedlity.

9. Bioactivity of dietary polyphenols

Inter-individual variation of the human gut microbiome means that there are many possible metabolic pathways that could be used by microbiota to contribute to bioavailability of dietary polyphenols (Manach et al., 2004). Due to this differential processing amongst humans, it is difficult to characterise specific mechanisms by which polyphenols are considered bioactive, and by which specific microbial species they are transformed (Cardona et al., 2013). Fig. 3 illustrates this.

As previously mentioned, there is diversity within the structure and function of dietary polyphenols. lower molecular weight polyphenols are likely to be immediately absorbed into the small intestine, whereas more complex polyphenols may reach the colon unchanged.

These larger weight polyphenols undergo enzymatic (α-rhamnosidase, β-glucosidase, and β-glucuronidase) transformation by the gut microbial community, breaking these structures into metabolites that can be absorbed, and are likely to be responsible for the health benefits

correlated (Fig. 2)with the consumption of polyphenol rich foods (Duda-Chodak et al., 2015).

It is important to note that whilst polyphenols are present in food in the free form, they are also found bound to other compounds, like within the dietary fibre matrix (Jackson & Jewell, 2017; Pandey & Rizvi, 2009). This makes them an interesting focus as a combinatorial product with prebiotics, many of which are dietary fibre. The stimulation of the gut microbiota by dietary fibre to produce specific microbial metabolites makes understanding the interactions between these compounds crucial (Kardum & Glibetic, 2018). It is plausible that polyphenols may also have a prebiotic effect (Alves-Santos et al., 2020), and that the dietary fibres present in the plant compounds might facilitate the transport of polyphenols to the colon.

The use of cereals as a food that contains both polyphenols and dietary fibre is a fantastic option, wherein bioavailability is extended and thereby the putative health benefits of polyphenol consumption is improved.

However, there is dietary fibre in many other foods, such as berries (Dreher, 2018), so this beneficial effect is not likely limited to just cereals.

There is an established, general, pattern of polyphenol metabolism, whereby natural polyphenols are transformed via a few general processes, such as deglycosylation, dehydroxylation and demethylation. Microbially modified phenolic metabolites will either be absorbed into the body or excreted in urine and faecal matter. Those that are absorbed may undergo Phase II metabolism before being circulated around the body (Mosele et al., 2015).

Research has shown that the main genera involved with phenolic degradation are *Clostridium* and *Eubacterium,* spp. which differs from the primary genera associated with intake of prebiotics (Selma et al., 2009).

It is also important to consider that the action of polyphenols on bacterial cells can differ –mechanisms will change depending on bacterial wall composition. The action may inhibit or encourage bacterial growth (Puupponen-Pimia et al., 2005). Compounds from green tea extracts have been seen to modulate certain bacteria (Jung et al., 2019), and blueberry extract has shown to increase bifidobacteria in the gut (Vendrame et al., 2011).

After consumption of flavonoids, sugar moieties may be removed and absorbed in the small intestine. Hydrolysis will occur in those flavonoids that are glycosylated, by action of β-glucosidase (amongst others), and these aglycones will then passively diffuse into epithelial cells (D'Archivio, 2010). It is important to note that, where rhamnose moieties exist, these flavonoids can reach the colon and may be hydrolysed by *Bifidobacterium* spp. through α-rhamnosidases (Bang et al., 2015).

Whilst, as mentioned, anthocyanins are one of the flavonoid groups, one of the ways they can be metabolised is by the transformation into a non-flavonoid, specifically phenolic acids (Keppler & Humpf, 2005). There are not many free circulating anthocyanins, and this is largely due to the metabolism by the gut microflora into phenolic acids (Han et al., 2021).

One of these phenolic acids, protocatechuic acid, is especially potent in its beneficial effects towards host heath. Though some research suggests that the primary precursor for the dihydroxybenzoic acids is the catechin group, protocatechuic acid has been consistently identified as a major metabolite of the anthocyanins (Wang et al., 2010). It has many putative health benefits, including tumoricidal properties, such as the induction of apoptosis in human leukaemia cells. It has also been shown to have significant neuroprotective effects, more specifically, protective against oxidative stress, and nitrosative stress (Winter et al., 2017). The bioactivity of the anthocyanins is thought to be largely due to these circulating microbial metabolites, which also remain longer in relevant tissues than the anthocyanins themselves (Tsuda et al., 1999). Protocatechuic acid is also more stable against metabolism by microflora than anthocyanins. (Fleschhut et al., 2006; Woodward et al., 2011).

Finally, the interaction between gut microflora and anthocyanin consumption is further solidified by in vitro studies suggesting that anthocyanins enhance the growth of *Bifidobacterium* spp. And *Lactobacillus-Enterococcus* spp (Hidalgo et al., 2012).

10. Molecular mechanisms related to polyphenol metabolites

As discussed, while there is variation in both the polyphenol metabolism and inter-individual microbial metabolism, most, if not all, polyphenols must reach the colon and undergo microbial or enzymatic transformations to ensure bioactivity and produce beneficial effects (Marín et al., 2015; Pandey & Rizvi, 2009).

One study looking at quinine metabolites directly linked the intake of polyphenol and metabolites to the stress response and specific gene regulation. Research showed that, by activating transcription factor Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), an adaptive stress response could be induced (Lee-Hilz et al., 2006). NRF2 has been highly associated with antioxidant effect genes that encode for antioxidant proteins and detoxification enzymes (Eggler et al., 2008)). This

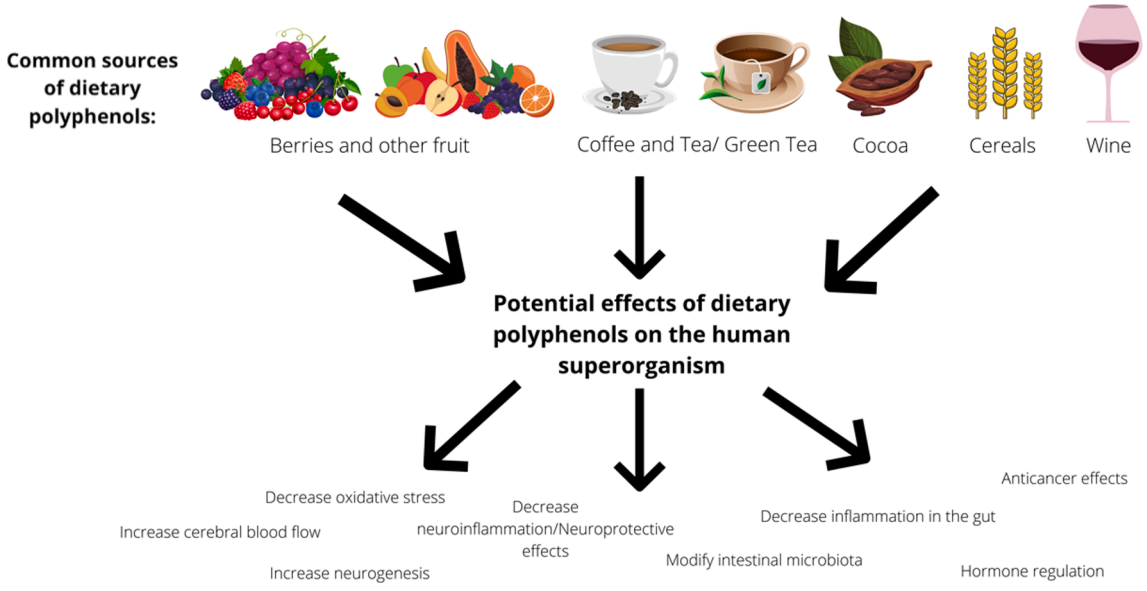

Fig. 2. Potential gut microbial associated effects of common dietary polyphenols on the human superorganism.

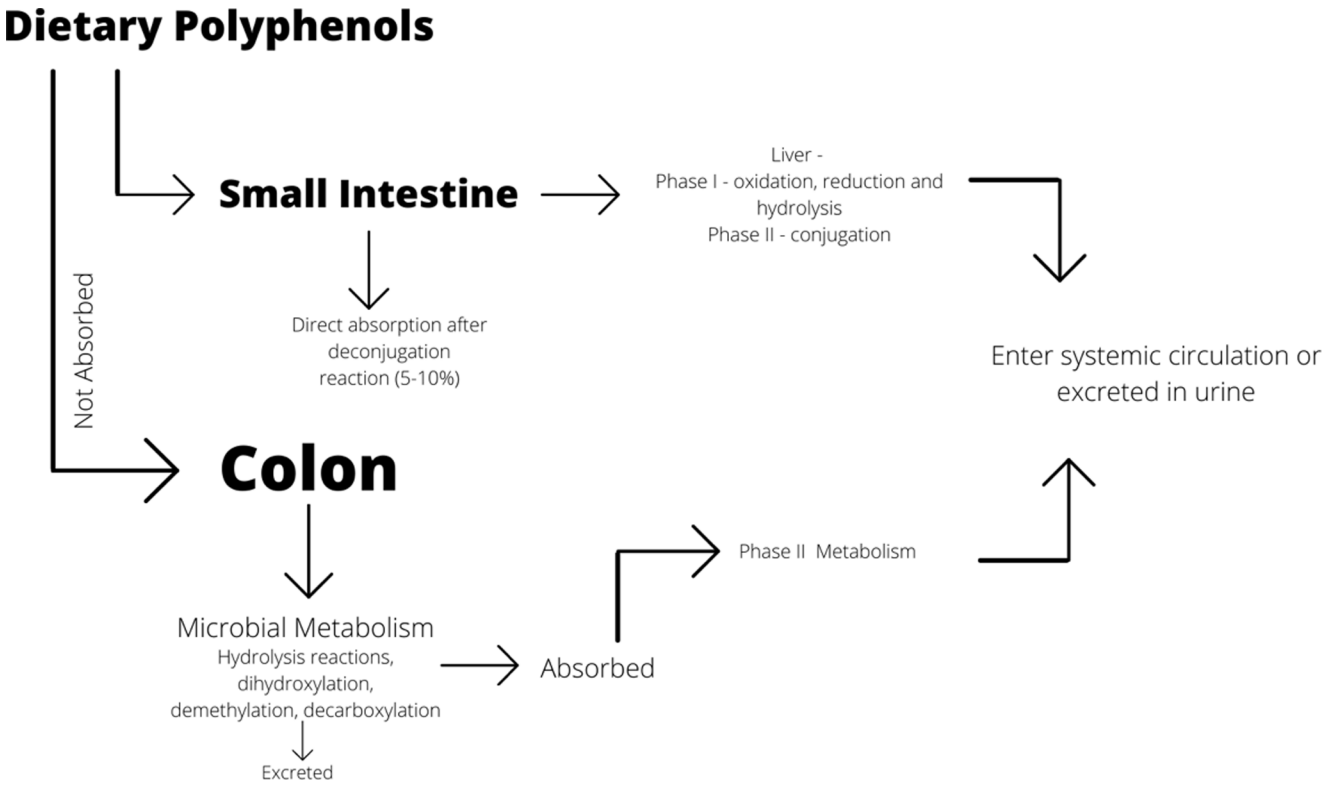

Fig. 3. Schematic illustration of the metabolic fate of dietary polyphenols in the human intestinal system. The routes shown include Phase I and Phase II metabolism, direct absorption into the small intestine, microbial metabolism, and entering into systemic circulation or excretion into urine.

association occurs because Nrf2 is regulated by a cysteine-rich protein, and quinones are able to act as acceptors that modify cysteine residues, leading to nrf2 activation and antioxidant response gene production (Eggler et al., 2009).

Many other polyphenols have been shown to potentially activate Nrf2, providing further evidence of the antioxidant and anti-inflammatory properties of polyphenols (Hussain et al., 2016). Because there is a two-way relationship between the gut microbiota and polyphenols (Ozdal et al., 2016), it is important that the specific mechanisms of metabolite action are further explored so that people in a disease state can benefit as effectively as possible from the intake of polyphenol rich foods.

Several studies have suggested certain polyphenolic compounds can benefit athletic performance (Myburgh, 2014) but literature has not, to date, provided a comprehensive review on benefits to military personnel.

Research consistently demonstrates the successful use of bioactive plant compounds, such as polyphenols, in reducing oxidative damage by reducing inflammation and influencing the immune response (Hussain et al., 2016). When experiencing extreme physical conditions such as endurance, fatigue or stress, one of the most damaging effects on the body and brain is from the increased oxidative damage caused by excess release of ROS (He et al., 2016; Hussain et al., 2016) As previously mentioned, polyphenols protect plants from oxidative damage and it is believed that these phytochemicals will have a similar effect in humans, albeit through different mechanisms (Pandey & Rizvi, 2009). Though artificial antioxidant supplementation may have some benefits, optimal doses of polyphenols have not been identified, making the likely success of supplements difficult to assess (Myburgh, 2014). This is because mechanisms and bioavailability of all polyphenols have not been accurately or completely described, partly due to variable interaction with the gut microbiota. Consequently, supplementation may be slightly less desirable (Cory et al., 2018; Myburgh, 2014) than consumption of whole plant foods. Furthermore, research also suggests that one of the benefits of consuming polyphenols in plant foods derives from their interaction with other nutrients; for instance the presence of other foodstuffs lessens post-prandial glucose spikes because the polyphenols interfere with carbohydrate digestion rates (Williamson, 2013). It would be useful to identify the specific bacterial gene expression associated with polyphenol intake and metabolism, but there has not been enough research in human studies to confirm this.

In such a substrate rich environment as the gut, it is difficult to identify specific bacterial expression because the gut microbiome is such a complex ecosystem, and it is known that cross-feeding occurs. It may, however, be possible to determine which substrates are metabolised first and which would be especially useful in terms of identifying interactions between carbohydrates and polyphenols. Pure culture studies have shown this in the case of NRF2, as mentioned above. However, this is difficult to extrapolate to the gut microbiota as we cannot separate out individual compounds and the experiments would also need to be repeated in a mixed community of microbes.

11. Specific foods with high polyphenol concentration

11.1. Blueberries

Studies have found that blueberries can reduce oxidative stress in athletes, possibly due to their antioxidant effect. Although this particular study was on athletes under heat stress (hyperthermic environments), athletes or military personnel under other stressful conditions such as high altitude may also benefit from a reduction in oxidative stress. This would suggest that blueberry supplements could be a useful addition to their diet. (McAnulty et al., 2004) Research has also demonstrated the effects of blueberries on metabolic diseases and suggests that the polyphenol content is responsible for the prevention of metabolic disease through modulation of the gut microbiota (Curtis et al., 2019).

Not only do blueberries seem to have an effect on the prevention of

metabolic disease, they are also associated with improved cognitive processing. A study showed that, in cognitively impaired adults, performance was altered after blueberry supplementation, with semantic access, memory and processing speed all improving (Krikorian et al., 2020). It is important to note that it is difficult to assess the absorption of blueberry polyphenols in studies such as this because, due to the phase II metabolites, there was no difference in urinary excretion of anthocyanins (Krikorian et al., 2020). This study also showed that those older adults who had ongoing blueberry intake before developing dementia maintained better cognition (Krikorian et al., 2020). As dementia is considered to be at least in part due to inflammation (Peila & Launer, 2006), it is likely that blueberries may have a similar impact on other inflammatory cognitive disorders, such as PTSD.

Supplementation of polyphenols in young people has also been shown to be beneficial; participants given an extract of grape and blueberry in one trial showed an improvement in cognition (Philip et al., 2019). This provides justification for further research into the use of polyphenol rich supplements to improve memory and attention, which would be of use to military personnel.

Not only do blueberries appear to play a role in the amelioration of cognitive impairments, but they also seem to improve 'healthy' cognition (Whyte et al., 2020). As it is well known that polyphenols rely heavily on the gut microbiota for bioavailability, it is likely that metabolism through the microbiota will be instrumental in this. Blueberry extracts have also been demonstrated to increase *Bifidobacterium* and *Lactobacillus*, shown through fluorescent in situ hybridisation (FISH) analysis (Molan et al., 2009).

11.2. Green tea

Results from several studies into green tea suggest that it would be an advantageous addition to a military diet. For example: green tea extract (GTE) may be beneficial for reducing the impact that cumulative fatigue has on athletic performance, through lessened muscle damaged and lower magnitudes of oxidative stress. Military personnel are often subjected to cumulative fatigue (Machado et al., 2018). This study also showed that GTE supplementation confers positive effects on neuromuscular function as a response to cumulative fatigue.

A 2018 study showed that, when green tea polyphenols were introduced into mice with high fat induced obesity, there were significant differences in differentially expressed genes (through KEGG pathway analysis) in ABS transporters and amino acid biosynthesis (Zhang et al., 2018). This suggests that intake of green tea polyphenols did have an effect on metabolic pathways and consequent gene expression. Though this was an artificial/environmentally induced microbial imbalance (through the high fat diet imposed on the mice) it provides a good basis for further human studies in the exploration of green tea polyphenols and metabolic pathways affected, especially when considering that the bioactivity of green tea polyphenols is made possible by transformation of compounds in the gut. This study was able to demonstrate that dysbiosis seen in the mouse gut after the high fat diet was mitigated by the intake of green tea polyphenols. Firmicutes were found to be less abundant and Bacteriodetes more abundant in faecal samples post intervention. However, there was much individual variation, probably as a result of the gut microbial variability between individuals. This symbiotic relationship between the gut microbiome and polyphenols needs clarification and further study (Zhang et al., 2018).

Other studies have demonstrated that the metabolites of green tea (for example the polyphenols catechins) are likely to be responsible for the beneficial health effects and may be biotransformed then metabolised further by the gut microbiota into phenolic acids (Higdon & Frei, 2003; Ozdal et al., 2016).

Research in dogs has demonstrated proportional changes within bacterial makeup of the gut microbiome, and this study similarly indicated that medicinal effects of the introduction of green tea polyphenols can be directly correlated with microbiota induced changes, for example a decreased expression of inflammatory cytokines (Li et al., 2020).

11.3. Cranberry

Cranberry has been shown to be beneficial in gut-related inflammatory diseases like Inflammatory Bowel Disease (IBD), where gut dysbiosis occurs(Wang et al., 2018). A study has shown that, by increasing the intake of dietary cranberry or the fruits, the severity of IBD symptoms may be reduced. A significant decrease in severity of dextran sodium sulfate (DSS)-induced colitis was observed within a mouse model, decreasing disease activity and increasing colon length after dietary consumption of cranberry. This study also demonstrated reduced levels of pro-inflammatory cytokines and alterations in the faecal microbiota. Whilst there was a decrease of diversity with the diseased group compared to healthy control, cranberry treatment not only reduced this decline in diversity but also reversed the changes (Cai et al., 2017). This reversal of change is particularly interesting when considering soldiers as, not only is prevention or reduction of gut related diseases useful, but also the corrective reversal of changes in gut bacteria (increasing the abundance of beneficial bacteria such as *Lactobacillus and Bifidobacterium* whilst decreasing potentially harmful bacteria), is both useful and encouraging. What is interesting about this particular study is its use of dietary whole cranberry, which has large amounts of indigestible fibre and polyphenols, both of which can reach the colon. While it has not been confirmed that the improvements were due to the polyphenols, it is important to consider that the dietary polysaccharides found in the cranberry could increase SCFA production and alter bacterial composition in mice (Cai et al., 2017).

Other research into the beneficial effects of cranberry includes a study using cranberry extract in diabetic mice to evaluate whether modulations of the gut microbiota play a role in reducing type 2 diabetes. Again, there was a potential metabolic impact of cranberry interacting with the gut microbiome, whether this be polyphenolic or because of a prebiotic effect. Whilst perhaps not at first glance directly relevant, this study did show that treatment with cranberry extract not only had an anti-diabetic effect but also alleviated intestinal inflammation (Anhê et al., 2015).

The primary 'active' polyphenols in cranberries are proanthocyanidins (Blumberg et al., 2013). *In vitro* studies have shown that these polyphenols have an antimicrobial effect, reducing *E. coli* levels in the gut (Harmidy et al., 2011; Roque, 2015) and, *in vivo*, they have been known to help reduce leaky gut, or dysfunction (Blumberg et al., 2013). This is where the use of cranberry extract could be particularly useful for the health and wellbeing of soldiers; not only is gut barrier dysfunction directly related to dysentery (König et al., 2016; Stewart et al., 2017), but it is also believed that stress exacerbates leaky gut (Vanuytsel et al., 2014; Wallon et al., 2008) which can then lead to inflammation and mental health conditions such as depression and PTSD. (Leclercq et al., 2016).

11.4. Cocoa

There has been a lot of research on the effects of cocoa polyphenols. Cocoa flavanols are able to cross the blood brain barrier and have been shown to improve cognition (Nehlig, 2013). Studies showed that cocoa flavonols were able to influence cognition in a number of ways although the exact mechanisms have not yet been fully understood. Research has shown that, through both direct and indirect actions, cognitive decline was reduced and general cognition, such as working memory, improved (Mastroiacovo et al., 2015; Socci et al., 2017). The flavonoids in cocoa, primarily epicatechin, have also been found to initiate neurogenesis (Valente et al., 2009). In common with other polyphenols, blood flow can be improved and, in the case of cocoa polyphenols, cerebral blood flow may be stimulated (Sorond et al., 2008), which may help reduce neuronal death.

Neurodegenerative diseases are often related to neuroinflammation

(Chen et al., 2016). Many studies have shown that polyphenols have anti-inflammatory effects throughout the body, and the same is likely to be true in the brain (García-Lafuente et al., 2009). Low grade inflammation associated with stroke (Zheng et al., 2003) and Alzheimer's is thought to be caused by an inflammatory cascade (McGeer & McGeer, 2003). Flavonols have been shown to reduce the effect of inflammation through cytokine release, amongst other processes (Leyva-López et al., 2016). Modulation of signalling pathways, like the MAPK signalling cascade, can affect neuronal function via inhibitory or stimulatory action that alters the target molecules, thereby altering gene expression (Spencer, 2007). One example of this comes from a study showing that oxidative damage could be prevented through anti-apoptotic action caused by direct action against the activation of caspase-3 (Schroeter et al., 2001).

Research has also been able to identify specific gene expression related to polyphenol intake where (when combined with ERK1/2) the polyphenol epicatechin regulated gene expression through activation of CREB. This aids memory and neuroplasticity by promoting an expression of genes including those involved in angiogenesis (Schroeter et al., 2006; van Praag et al., 2007).

Although not directly related to polyphenol intake in military personnel under stress, studies have found that the intake of dark chocolate (i.e. cocoa) reduced urinary excretion of the stress hormone cortisol (Martin et al., 2009). However, research also concedes that chocolate feels comforting so some of the mood boosting effects may be psychosomatic (Parker et al., 2006). However, cocoa was seen to normalise the gut microbial activity seen in stressful situations, modifying the gut microbiome within two weeks (Martin et al., 2009).

Cocoa flavanols have also been seen to directly enhance pathways that increase brain-derived neurotrophic factor which, again, improves neuronal growth and health (Neshatdoust et al., 2016). Bacteria that have been identified as part of the gut microbial metabolism for cocoa polyphenols are *E. coli*, *Bifidobacterium* spp. (also found increased in faecal samples after the consumption of cocoa), *Lactobacillus* spp., *Bacteroides* spp., and *Eubacterium* spp (Cardona et al., 2013). Research has shown that beneficial bacteria are increased and pathogenic species like *Clostridium* are decreased after the intake of polyphenols (Duda-Chodak et al., 2015).

It is, however, important to mention that cocoa is not the only food group that includes polyphenols that cross the blood brain barrier. In fact, in rats that had supplementation with blueberry polyphenols, specific polyphenols were subsequently found in the brain; anthocyanins were found in the cortex and hippocampus (Andres-Lacueva et al., 2005).

Whilst research has been carried out on individual polyphenols, most research focusses on the entire plant, that is a polyphenol mixture. There is likely much interaction, or crosstalk, between different compounds and phytochemicals within individual plants, and also within foods consumed alongside them.

It may be less useful to discuss research that focusses on individual polyphenols than those studies considering the effects of whole plant foods. The interaction of different foods and the gut microbiota should be studied, but also more research is needed into whether or not other foods consumed with polyphenols affect bioavailability and activity of these chemicals. Furthermore, given that research suggests certain food types improve the health of the gut microbiota, it may be worth considering eliminating or reducing those foods that cause detriment to it, or rather cause dysbiosis (Brown et al., 2012). Otherwise, any benefits from introducing prebiotics and polyphenols to a diet could be negated.

Controversially, a recent study found that a 15 day consumption of a blend of flavonoids from cocoa, blueberry and green tea exerted none of the expected effects on aspects of the gut microbiome normally associated with good health, such as SCFA concentrations, gut inflammation, or diversity of the gut microbiome (Kung et al., 2020). This is interesting as studies that have looked at separate contents of these flavonoids have found them to have a considerable impact. It may be that more dramatic effects are seen when these foods are combined with prebiotic interventions. In this study, liquidised extracted samples were used in the intervention, so it may also be that whole food intake is more beneficial. Furthermore, in this study, only one faecal sample was taken between days 9–11 of the study, and a study in gnotobiotic mice showed that it might take 14 days to see differences in the gut microbiome after an increase of plants in the diet. Finally, it should also be taken into account that we may not see a massive change in the gut bacteria of people who already consume polyphenols, or rather those athletes who are likely to already have a good diet. These factors plus a fairly small sample size may be the reasons for this unexpected result. Notwithstanding, more research is needed to further investigate such findings.

12. Pharmacomicrobiomics

Not only is it important to explore nutrition as a treatment and preventative measure for PTSD, but understanding the impact of the gut microbiota on metabolism is also crucial given the potential differences in metabolism of pharmacological treatments in individuals. Currently available medications, such as Selective Serotonin Reuptake Inhibitors (SSRIs), are limited in their benefit; they are not specifically designed for PTSD, and will often have less than a 30% patient full remit (Berger et al., 2009). Exploring the optimisation of drugs through pharmacomicrobiomics could be a way to improve patient remit and drug efficacy. It is also important to consider that drugs for PTSD have been shown to be effective prophylactically (Litz, 2008; Roque, 2015). Given that nutritional interventions have had the same effect in disorders such as depression, it is reasonable to posit that a nutritional intervention could also be successful prophylactically in PTSD (Rechenberg & Humphries, 2013). Research has suggested that treating PTSD earlier or at the subclinical level is beneficial in terms of the reduction of symptoms and developmental trajectory of the disorder (Korte et al., 2016).

Pharmacomicrobiomics considers the interplay of inter-individual microbiome variation and the response to drugs (Doestzada et al., 2018). Long term perturbations such as stress can disrupt the gut microbiome environment, causing detriment to the homeostatic environment surrounding the gut-brain axis (Carabotti et al., 2015). This disturbance is likely to worsen hypothalamic–pituitary–adrenal (HPA) axis function and immune function, given the ways in which the gut ecosystem interacts and triggers physiological changes in the brain.

Differences in an individual's drug response can not only cause detriment economically to society if it causes the treatment to fail, but can also seriously affect a patients wellbeing (Sultana et al., 2013). Improving the efficacy in the kinetics of drugs is always desirable (Sharma et al., 2019). However, given that personalised medicine is expensive and time consuming, (Vogenberg et al., 2010) finding a nutritional intervention that could increase beneficial bacteria in the gut, reduce the detrimental effects of certain disorders and potentially increase the efficacy of certain drugs could be of huge benefit.

13. Conclusion

By using the gut microbiota as a therapeutic target to exploit the bidirectional gut-brain axis, it may be possible to address neuropsychiatric conditions, such as PTSD. This is very exciting, as diet is one of the most modifiable factors of the gut microbiota, at all points in life, regardless of health status (Leeming et al., 2019). Effective remedies are urgently needed for the negative consequences of stress, dysentery and PTSD seen within military personnel. There appears to be no detriment to health from increasing authentic prebiotic and polyphenol intake in the diet, especially if it is through consumption of whole foods rather than supplementation of individual polyphenol extracts. The use of prebiotics and polyphenols to treat neuropsychiatric and physical conditions in military personnel looks very promising. That said, more research is needed to identify specific bacterial metabolites and specific bacterial gene expression for combinatorial polyphenol food groups

before safety and efficacy can be confirmed.

14. Ethics statement

No animal or human experimentation was conducted in this review manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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