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Review Article

The Effects of Green Tea Bio-active Components on Human Gut Microbiome: Implications in Cardio-metabolic and Mental Health

Nicola Stanislawska[1] Joanna Michalina Jurek[2*]

[1]Akademeia High School, Urszula Ledochowska 2, 02-972, Warsaw, Poland; [2]Vall d'Hebron Research Institute (VHIR), Mediterranea Research Building, Division of Rheumatology, Research Unit in ME/CFS and Long COVID (Lab 09–Box 02), Passeig de la Vall d'Hebron 119-129, E-08035–Barcelona, Spain

ABSTRACT

Different dietary components, in particular those of plant origin, have been implicated in maintaining appropriate cardio-metabolic and mental health. Although many mechanisms have been proposed, certain phytochemicals, such as polyphenols, by promoting appropriate gut microbiome function, are thought to improve metabolic health indices and reduce the risk of chronic diseases such as depression, obesity, and diabetes. Polyphenols, a diverse group of over 8,000 bio-actives, dominated by those of plant origin, have been associated with antioxidant, anti-inflammatory and anti-proliferative properties, prompting research efforts into investigating sources of these phytochemicals. A significant amount of plant bio-actives are found in many fruits and vegetables, however certain beverages, like tea, can also act as a rich source of them. To date, many studies have demonstrated that regular intake of tea, in particular green tea, may help with glycemic control, boost metabolism as well as lower subjective feelings of stress and anxiety. In addition, there is also growing evidence indicating that these effects may be linked with the influence of green tea polyphenols on gut microbiota composition, which has been demonstrated to increase the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, while hindering the growth of specific potentially harmful species like *Bacillus cereus*, *Campylobacterjejuni*, *Clostridium perfringens*. These modulating properties may further help to correct microbial dysbiosis, which is a contributing factor to the development of various diseases, including obesity, type 2 diabetes, metabolic syndrome, Cardiovascular Disease (CVD) and depression. Therefore, based on the existing experimental and epidemiological research, this study aims to review the current evidence on green tea bioactive compounds, including polyphenols, and their effects on both cardio-metabolic and mental health mediated through gut microbiome.

Keywords: Polyphenols; Green tea; Gut microbiota; Human health

Abbrevations: BAI: Beck Anxiety Inventory; BMI: Body Mass Index; CVD: Cardiovascular Disease; D: Day; DL: Deci liter; EC: Epicatechin; ECG: Epicatechin Gallate; EGC: Epigallocatechin; GC: Gallocatechin; GCG: Gallocatechin Gallate; GLP-1: Glucagon Like Peptide 1; HARS: Hamilton Anxiety Rating Scale; HbA1c: Glycated Haemoglobin; HDL: High Density Lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; LDL: Low Density Lipoprotein; IL-6: Interleukin-6; LPS: Lipopolysaccharide; MD: Mediterranean Diet, mg: milli gram; mmHg: millimetres of mercury; NO: Nitric Oxide; SCFA: Short Chain Fatty Acids; TMAO: Trimethylamine N-Oxide; TNF- a: Tumour Necrosis Factor-Alpha; STAI: State Trait Anxiety Inventory; VAMS: Visual Analogue Mood Scale; WC: Waist Circumference; WHO: World Health Organization

Correspondence to: Joanna Michalina Jurek, Vall d'Hebron Research Institute (VHIR), Mediterranea Research Building, Division of Rheumatology, Research Unit in ME/CFS and Long COVID (Lab 09–Box 02), Passeig de la Vall d'Hebron 119-129, E-08035–Barcelona, Spain; E-mail: joanna.michalina.jurek@gmail.com

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INTRODUCTION

The gut microbiota present in the human gut is a complex and diverse microbial community consisting of 10^14 microorganisms (Thursby, et al.) with the most abundant being phyla *Firmicutes* and *Bacteroidetes*, representing approximately 90% (Rinninella, et al.) of the total gut population. While the composition of the gut microbiota in healthy adult individuals has been found to remain largely stable over time, exposure to various factors may influence the bacterial population, including infections, the use of dietary supplements (e.g probiotics, prebiotics, multivitamins), antibiotics and other medications (e.g anti-inflammatory and steroid drugs), as well as changes in lifestyle and dietary habits (Rodriguez, et al.). If such influences are significant, they may lead to the dysregulation of the gut microbial network, resulting in as state of imbalance known as dysbiosis. Gut dysbiosis, if not regulated, has been linked to an increased risk of developing certain chronic diseases, including Inflammatory Bowel Disease (IBD), allergies, obesity, diabetes, and other metabolic syndromes, as well as autism and colorectal cancer (de Gruttola, et al.). Furthermore, given a bidirectional link between the gut and brain, dysbiosis may explain the co-occurrence of gastrointestinal and mental conditions as, for example; many patients diagnosed with irritable bowel syndrome often suffer from depression and/or anxiety disorders (Irving, et al.). It is therefore crucial to maintain a healthy gut microbiota composition throughout life to optimize human health [1-5].

To date, many approaches have been proposed for the interventional modulation of the human microbiota, with probiotics (live microorganisms) and prebiotics (non-digestible carbohydrates) supplementation being the most common (Rodriguez, et al.). However, emerging evidence suggests that modifying diet composition, such as altering proportions of consumed macronutrients (e.g., proteins, carbohydrates and fats) may also be an effective means of changing the composition of the gut microbiota in the large intestine (Walker, et al.). In particular, an increase in the consumption of plant based foods has been shown to help control proper gut microbiota balance. A diet rich in fresh fruit and vegetables, being a source of various phytochemicals, such as polyphenols, oligosaccharides and dietary fibre, has been associated with beneficial health effects, including reduced risk of chronic diseases (van der Merwe). Additionally, a growing interest in the potential use of botanical and herbal remedies, either as a part of the diet (e.g., beverages, juices, smoothies, oils) or dietary supplements (e.g., capsules, powders with extracts pursue research efforts into evaluation of these preparations in the disease management and prevention). Such remedies, being rich in various functional bio-actives with health-promoting properties, may aid in the prevention of major illnesses linked to metabolic and mental conditions (Belardo, et al.). One of such examples of widely consumed sources of plant bio-actives is tea, with its regular consumption as a beverage being associated with favourable health effects in terms of metabolic and glycemic control through the regulation of the gut microbiota (Perez-Burillo, et al.) [6].

Therefore, the aim of this review is to evaluate the latest evidence from epidemiological studies in order to investigate the effects of tea polyphenols on gut microbiota and associated health outcomes, with a primary focus on cardio-metabolic and mental indices.

Gut microbiota and its importance for maintaining optimal health

The human microbiota is defined as the collection of microorganisms in a particular location within the body, such as the gastrointestinal tract (referred to as the gut microbiota), while the term microbiome encompasses the microbiota and its genetic material, metabolites, and environment (Clapp, et al.) [7]. The gut microbiota, given the complexity and diversity of its microbial communities, plays a vital role in maintaining overall human health and modulating activities linked to the gastrointestinal tract and central nervous system functions (Du, et al.) [8]. To date, studies have demonstrated that disruption of the gut microbiome functioning, especially in the early life, can be associated with an increased risk of gastrointestinal and mental conditions, including obesity and depression. For example, patients diagnosed with Irritable Bowel Syndrome (IBS) typically experience co-occurring depression and/or anxiety disorders (Irving, et al.) [9]. Moreover, the gut microbiota composition of individuals diagnosed with mental health disorders, such as Alzheimer's, Parkinson's disease and Schizophrenia differs significantly from that of healthy individuals (Keshavarzian, et al., Vogt, et al., Golofast and Vale) characterised by increased *Bacteroidetes* followed by decreased *Firmicutes* and *Bifidobacterium* found in Alzheimer's patients (Vogt, et al.) [10,11].

Although many factors have been found to influence gut microbiota composition and it's functioning, dietary habits are recognized as one of the most important contributors. Observational studies have shown that highly processed diets, such as the Western style diet, have been associated with a decreasing number of health promoting microorganisms, like *Firmicutes* and an increase in potentially harmful species, such as *Bacteroides*, which have been shown to promote immune activation and chronic inflammation in the body (David, et al.) [12]. In contrast, vegetarian diets are associated with higher diversity and well-functioning gut microbiota, characterised by the domination of species such as *Ruminococcus*, *Roseburia*, and *Eubacterium*, transforming the insoluble dietary fibres (prebiotics) into bioactive metabolites, which promote cardio-metabolic health (Walker, et al.) [13].

One example of a dietary pattern which supports a well-functioning gut microbiota is the Mediterranean Diet (MD)

(Wu, et al., Jeffery, et al.) [14,15]. Recent studies have shown that a diet with a high content of plant based foods, in particular fruits (e.g., berries, grapes), nuts (e.g., hazelnut, walnut, almond, pecan), beans and vegetables (e.g., artichokes, chicory root, red onions, spinach), whole grain cereals, with beverages containing high content of polyphenols (e.g., red wine, tea) (Batiha, et al.) (Pandey, et al.) can favourably modify the microflora community, additionally preventing colonisation by opportunistic pathogens (Kawabata, et al., Lee, et al., Tzounis, et al.) [16-18]. Interestingly, individuals who follow MD, by consuming a higher proportion of plant based foods, have been found to have a higher percentage of Short Chain Fatty Acids (SCFAs) producing bacteria in the gut, whereas those with poor adherence to the MD have been shown to possess a higher concentration of Trimethylamine N-Oxide (TMAO) (de Filipps, et al.) which is known as a cardio-metabolic risk marker (Videja, et al.) [19,20]. TMAO is produced in the gut certain bacteria from dietary precursors, such as L-carnitine, betaine and choline and the consumption of a diet rich in saturated fats has been shown to lead to increased TMAO levels in humans (Boutagy, et al.) [21].

Microorganisms residing in the gut play an important role in the utilization of polyphenols from a variety of plant based foods. The complex structure of plant phenolics, by limiting their bioavailability and absorption rate in the gut, cause them to remain in the gut for an extended period of time in comparison to other nutrients, thereby allowing polyphenols to directly interact with microbial communities in the gastrointestinal tract (Duda-Chodak, et al.) [22]. Bacterial transformation of dietary polyphenols results in the production of a variety of health promoting metabolites, including SCFAs, as well as other bio-actives like phenolic acids, and urolithins, of which potent anti-oxidative and anti-inflammatory properties may help prevent against the development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases (Graf, et al., Arts and Hollman) [23].

Tea as source of polyphenols

Although thousands of years old, tea continues to be renowned as one of the most consumed aromatic beverages in the world. Made from the infusion of the leaves of the *Camellia sinensis* plant, the beverage has been utilized in traditional Chinese medicine for over 3000 years (Xing, et al., Perez-Burillo, et al., Hinojosa-Nogueira, et al.) [24-26]. More recently, the rise of global trade has increased its popularity in the Westernised world, with more research conducted into the relationship between tea consumption and human health (Hinojosa-Nogueira, et al.) [27].

Tea varieties available to consumers vary depending on the world region and preparation method, with the most common of these types being black tea and green tea, and less known varieties, such as wulong (oolong) tea, white tea, puer (pu-erh) tea and dark tea. Different preparation methods of teas significantly impact their appearance, taste as well as phenolic content. For example, white and green teas do not undergo fermentation, compared to dark varieties, like oolong and black teas which are fermented (Islam, et al., Kujawska, et al., Lv, et al., Sanlier, et al., Hilal, et al., Zheng, et al.) [28-32]. The process of preparation is reflected in the tea composition, as white and green teas are abundant in the polyphenols, especially catechins and their derivatives (Tang, et al., Zhao, et al., Luca, et al., Satoh, et al., Yang, et al.) [33-38]. While fermented dark teas contain polyphenols (catechins) in their oxidised versions, known as Theaflavins, Thearubigins, and Theabrownins (Lv, et al., Koch, et al., Tang, et al.) [39-41].

To date, epidemiological evidence demonstrates various health benefits resulting from habitual tea drinking, especially in the case of green tea consumers. Green tea is characterized by its light, clean taste and pale green tint resulting from a unique method of preparation conducted with low access to oxygen. The preparation method of green tea leaves is detrimental for its health promoting properties; the leaves are immediately steamed under high temperatures or roasted to prevent fermentation, leading to the inactivation of the oxidative enzyme polyphenol oxidase, which protects its polyphenolics from being oxidised (Wang, et al.) [42]. Moreover, among phenolics, green tea is a rich source of amino acid, known as L-theanine, which, being able to penetrate the blood brain barrier, can impact brain function and promote good mental health and aid prevention against neurodegenerative diseases and depression. Interestingly, L-theanine has also been found to reduce the stimulatory effects of caffeine, while creating feelings of alertness, mood, and concentration (Unno and Nakamura) [43]. For example, individuals with no reported psychiatric illness, given L-theanine supplementation over 4 weeks had improved verbal fluency and executive function, as well as lower anxiety and depressive symptoms with further improvement in the sleep quality (Hidese, et al.) [44]. These findings are consistent with other studies, which also reported beneficial effects of regular green tea consumption on cognition, explained as the effects of caffeine and L-theanine (Mancini, et al.) [45].

LITERATURE REVIEW

Polyphenols in green tea

The health promoting effects of green tea are mainly attributed to its polyphenol presence green tea contains a high concentration of active substances which have been found to have a positive influence on human health through protective, antioxidant properties that reduce free radical cell damage (Panche, et al., Batiha, et al., Yeh, et al.) [46-48]. Moreover, the antioxidant properties of green tea have been found to have the ability to hinder or stimulate the growth of various bacteria. Due to the diverse population of bacteria in the human gut microbiome, polyphenolic compounds present in green tea can assist in the treatment of various gut microbiome related illnesses, including colorectal cancer or obesity (Perez-Burillo, et al.) [49].

Catechins, a type of flavonoids, are the most abundant polyphenol in green tea, representing between 30–40% of the tea composition (Wang) [50]. Green tea catechins predominantly include catechin, Epicatechin (EC), Epicatechin Gallate (ECG), Epigallocatechin (EGC) and its stereoisomer Gallocatechin (GC), EGCG and its stereoisomer Gallocatechin Gallate (GCG) (Amarowicz, et al., Anderson, et al., Muzolf-Panek, et al., Fathima, et al.) [51-54]. Among these, Epigallocatechin Gallate

(EGCG) is the most abundant and can account for ~50% of the total catechin content in green tea extracts.

EGCG has been associated with a range of health promoting effects which include antitumor, antioxidant, anti-inflammatory, anti-diabetes, anti-obesity, anti-hypertension, anti-aging, anti-viral, antibacterial properties (Musial, et al., Rawangkan, et al., Unno and Nakamura) [55-58]. Green tea flavonoids have been found to show beneficial effects with respect to cardiovascular health due to their ability to regulate lipid and glucose flavonoids modification, which may alter lipid metabolism (Zern, et al.) [59], inhibit Low Density Lipoprotein (LDL) oxidation (Jeong, et al.), reduce atherosclerotic lesion formation (Fuhrman, et al.) inhibit platelet aggregation (Hubbard, et al.), decrease vascular cell adhesion molecule expression (Ludwig, et al.), improve endothelial function (Hallund, et al.) and reduce blood pressure (Hodgson, et al.) [60-65]. Similarly, to L-theanine, EGCG can also cross the blood brain barrier and influence physiological functions in the brain (Unno and Nakamura) [66]. Experimental research has shown that EGCG obtained from green tea can decrease the risk of cognitive decline and dementia through the activation of nerve cells. Interestingly, EGCG also provides metabolites during microbial transformation in the gut which may additionally bring long lasting benefits linked to stress-reduction (Unno and Nakamura) [67].

The impact of green tea polyphenols on the gut microbiota

Apart from the benefits of polyphenols attributed to their antioxidant properties, catechins are also associated with hindering or stimulating the growth of bacteria in the human gut microbiome (Martin, et al.) [68]. Experimental studies have shown that tea catechins can be metabolized by microorganisms residing in the gut, thereby affecting the microbiota composition in a favorable manner, beneficial for human health, reducing the risk of certain conditions (Chen, et al.) [69].

For example, green tea catechins have been shown to act as prebiotics (Gibson, et al.) and promote the growth of probiotic bacteria strains (Martin, et al., Wang, et al.), such as *Bifidobacterium* and *Lactobacillus* (Zhang, et al.) [70-73]. The increased abundance of these strains in the gut is associated with beneficial health outcomes, promoting gut homeostasis (van Baarlen, et al., Ruiz, et al.) [74,75]. These effects are attributed to *Bifidobacteria* and *Lactobacilli* ability to produce SCFAs, in particular acetate, which being utilised by other SCFA producing bacteria, can promote their colonisation of the gut, while reducing the opportunities for potential pathogens to grow. Expansion of butyrate producing bacteria as the result of the cross feeding process, increases availability of butyrate, which is an example of a SCFA, which is essential for the maintenance of the intestinal lining and mucosal lining, as well as preventing against gut inflammation (Okumura, et al.) [76].

The regular consumption of green tea followed by an increased intake of its polyphenols has been shown to significantly increase the abundance of *Bifidobacteria* and *Lactobacilli* in the gut (Axling, et al.) [77]. This have been supported by experiments showing that treatment with EGCG and its derivatives, such as Gallocatechin Gallate (GCG) and EGCG 3"-methyl preparations, has been shown to significantly increase the abundance of *Bifidobacterium* spp, *Lactobacillus*, while exhibiting an inhibitory effect on the growth of *Bacteroides–Prevotella*, *Clostridium histolyticum* and *Eubacterium clostridium* species in the human intestinal microbiota *in vitro*. Interestingly, this change in the gut microbiota community was reflected in the total SCFA production, which also increased compared to the control, thereby suggesting that EGCG derivatives obtained from tea may have potential prebiotic favourably modulating intestinal microbiota and contributing to the improvements of host health (Zhang, et al.). Similar effects leading to increased *Bifidobacteria* have been observed in humans, who drink a daily average of 2 to 5 cups of green tea for 10 days (Yuan, et al.). In addition, an increase in the colonisation of *Lachinospiraceae*, *Ruminococcaceae*, *Dorea*, *Roseburia*, *Feacalibacterium*, *Eubacterium*, *Blautia* and *Coprococcus* strains was found in the green tea consumers, followed by reported increased availability of SCFA, which was proposed as a potential mechanism preventing against inflammation in the gut. Studies to date have demonstrated that certain SCFA, especially propionate and butyrate, have, by reducing stimuli induced expression of adhesion molecules, suppressing monocyte/macrophage and neutrophil recruitment and lowering pro-inflammatory mediators (e.g., interleukin-6 (IL-6), Tumour Necrosis Factor Alpha (TNF-A)) production, which may help to modulate immune responses following inflammation and in the same time restore intestinal homeostasis through anti-inflammatory actions (Donohoe, et al., Correa-Oliveira, et al.) [77,78]. These benefits were also confirmed in experimental studies investigating immuno-modulating capabilities of butyrate, confirming butyrate ability to reduce inflammation in a mouse model of colitis, as well as in patients with ulcerative colitis. These effects may be especially relevant for the management and prevention against cancer (e.g., colorectal cancer) and chronic inflammatory gut conditions (e.g., IBD, ulcerative colitis, leaky gut syndrome), as, in several studies, these patient groups have been reported to have reduced levels of dominant SCFAs-producing bacteria (Joossens, et al., Kumari, et al., Takahashi, et al., Wang, et al., Pascal, et al.) [79-83]. Nevertheless, further research needs to be carried out in order to determine whether green tea polyphenols could help modulate the gut microbiota in these conditions.

Furthermore, catechins in green tea have demonstrated potent antibacterial properties, which were linked to their ability to reduce the growth of potentially harmful bacteria for human health, including *Bacillus cereus*, *Campylobacterjejuni*, *Clostridium perfringens*, *Escherichia coli*, *Helicobacter pylori*, *Legionella pneumophila* and *Mycobacterium* spp (Zhang, et al.) [84]. The inhibitory effect of green tea polyphenols on these species is attributed to its ability to disrupt the cell membrane of pathogens. For instance, EGCG found in green tea extracts, has been found to bind the peptidoglycans present on the gram-positive bacterial cell membranes, leading to their rupture (Yoda, et al.) [85]. This is highly relevant to inhibitory effects on Staphylococcus species, which being classified as gram positive bacteria, possess a thick cell wall made of 30–50 layers of

peptidoglycan, additionally covered by a rigid envelope providing protection against unfavourable environmental conditions (Morse, et al.) [86]. Consequently, treatment with EGCG, through direct binding to peptidoglycan on *S. aureus* organism cell wall, induced damage of the structure (Yoda, et al.) [87]. Ultimately leading to the elimination of this bacterium which was no longer able to tolerate high ionic strength and low osmotic pressure in the external environment (Zhao, et al.) [88]. However, it must be mentioned that some gram-positive bacteria are not negatively affected by similar treatment, which highlights the need for further research that would contribute to understanding the selective antibacterial effects of green tea polyphenols.

Green tea and human health

Most health benefits of green tea are associated with its high content of a range of different bio-actives, as tea may contain more than 700 chemicals such as amino acids, vitamins (C, E and K), flavonoids, caffeine, polysaccharides (Bag, et al.) [89]. In addition, green tea, being prepared from fresh leaves, contains a higher polyphenol content than other types of tea (Khairudin, et al.) which may explain why epidemiological studies have observed positive effects on human health in regular tea consumers, including improvements in lipid profile, normalizing blood pressure and lowered glucose levels in the blood (Bag, et al.) [90,91].

Several studies have investigated the effects of green tea consumption on the gut microbiota and overall health measures in apparently healthy adults. For example, the incorporation of a daily intake of 1000 ml of green tea instead of water after 10 days led to favorable changes in the gut microbiome composition in the individuals aged between 33 and 70 years of age, whom prior to the intervention described themselves as non-habitual tea drinkers. The results have found that despite inter individual differences in the *Bifidobacterium* species among subjects, an overall tendency for the proportion of *Bifidobacteria* was increasing in those consuming green tea, due to its prebiotic properties (Jin, et al.) [92]. Similar findings were reported in the dietary intervention with ready to go green tea drinks. In a study, an acute intake of a 400 ml portion of the green tea increased the bioavailability of flavan-3-ol catabolites, which were delivered within the tea, including microflora-derived polyhydroxyphenyl-γ-valerolactones, thereby suggesting that regular consumption of green tea beverages is a good source of bio-actives, that, utilized by colonic microbiota, can provide numerous benefits for the human body (Del Rio, et al.) [93].

Green tea and cardio-metabolic benefits

Observational studies conducted among frequent tea consumers, which included predominantly native populations of South Asian and South American origin, have demonstrated that regular daily intake of tea beverage may benefit those individuals who are predisposed to diabetes (Alkhatib, et al.) [94]. For example, the consumption of Mauritian green tea, being high in polyphenolic, has been shown to improve cardio-metabolic measures among the Mauritian population, as the regular Mauritian tea intake was linked with lower C-Reactive Protein (CRP) levels (Bahorun, et al.) as well as decreased fasting blood glucose levels (reduction by 18.4%), triglyceride levels (reduction by 35.8%), and improved lipid profile demonstrated as reduced LDL/HDL cholesterol ratio (reduction by−16.6%) followed by a significant increase of antioxidants in blood plasma (Bahorun, et al.) [95,96]. Observational studies have shown that regular tea consumption, being equal to or more than 3 cups a day, was linked with a lower risk for developing type II diabetes, compared with lower intakes, or not drinking tea at all (Yang, et al.) [97].

Diabetes

Diabetes mellitus is a group of physiological dysfunctions characterized by a hypoglycemic state, insulin deficiency, inadequate insulin secretion, or excessive glucagon secretion. According to The World Health Organization (WHO) classification, there are four types of diabetes mellitus (both type 1 and type 2), "other specific types", and gestational diabetes (Patil) of which diabetes type 2 is the one being the most commonly observed in westernised societies. Although many risk factors have been implicated in diabetes development, genetics, a sedentary lifestyle, and diet are the major modifiers on glycaemic responses in the body. There is also growing evidence that the microbiome may influence the onset and development of this disease (Sikalidis and Maykish), with studies showing that altered gut microbiota homeostasis can have a detrimental role in carbohydrate metabolism, which could eventually lead to diabetes (Knip and Siljander). Furthermore, the metabolites of microbial origin, such as SCFAs, amino acid derivatives, and secondary bile acids, are implicated in many metabolic and immune processes, which, when altered, could lead additionally lead to the development of diabetes (Zhao, et al.) [98-105].

Diabetes, as a chronic disease, requires the incorporation of continuous treatment strategies that aim to improve glycaemic control of individuals and prevent systemic complications. Lifestyle interventions including diet modification and the incorporation of dietary supplements help to reduce the frequency and severity of hypoglycaemia and improve insulin sensitivity. In this case, use of natural compounds of plant origin, such as tea polyphenols has been also found to be beneficial. The anti-diabetic properties of green tea are attributed to its bio-actives, predominantly theaflavins, caffeine, catechins, and polysaccharides, because of their ability to influence signal cascades and critical components associated with insulin, blood sugar levels, and energy metabolism regulation (Bag, et al.) [106-108]. Interestingly, green tea catechins have been shown to actively modulate the activity or expression of several receptors and enzymes involved in the absorption, metabolism transport and synthesis of carbohydrates. Digestive enzymes are inhibited in vitro by green tea catechins, including alpha-amylase, intestinal sucrase, alpha-glucosidase, and gastric H^+, K^+-ATPase. In addition, green tea bio-actives, such as EGCG, may also have beneficial impacts on the intestinal flora. In experimental settings, green tea bio-actives have been reported to improve the parameters of diabetic mice and to increase the *Firmicutes/Bacteroidetes* ratio and that of the *Lactobacillus* species (Park, et al.), whereas at family level,

EGCG increased *Christensenellaceae* and decreased the *Enterobacteriaceae* and *Proteobacteria* proportions (Banerjee, et al.). Interestingly, in a clinical study conducted on obese individuals, EGCG combined with caffeine at low doses demonstrated synergistic effects on altering gut microbiota, including decreased *Firmicutes* level and increased *Bifidobacterium* level. In addition, the intervention also increased the production of SCFAs, including acetic acid, propionic acid and through promoting the release of unconjugated bile acids and enhanced faecal bile salt losses (Zhu, et al.) [109].

Previous epidemiological studies conducted to assess the effect of regular green tea intake on diabetic populations vary in the results, therefore more research must be conducted in order to confirm the effectiveness of the use of green tea bio-actives in the management of type 2 diabetes. So far, the existing evidence has shown that the daily consumption of more than 3 to 4 cups of tea decreased the risk of type 2 diabetes by one-fifth, compared to individuals who do not drink tea (da Silva Pinto, Suzuki, et al.). Interestingly, those individuals who regularly consume green tea, but not black tea, had significantly reduced fasting glucose levels in the blood, when compared to those who drink water (Kondo, et al.) [110-112].

According to clinical interventions with green tea, studies are limited to only a few direct investigations examining the effect of green tea supplementation in patients with type 2 diabetes. These studies indicate that individuals receiving supplementation with green tea catechins with doses ranging from 80 to 1344 mg/d over periods from 3 weeks to 12 months may have better glycemic control, demonstrated by significantly lowered fasting blood glucose by 44 mg/dL (95% CI:-2.26, −0.62 mg/dL), however with no significant improvements on fasting insulin and HbA1c (glycated haemoglobin) values. Overall, authors conclude that green tea supplementation can significantly reduce fasting glucose short term, however, does not have a significant impact on fasting insulin and HbA1c (Xu, et al.) [113].

Interventions with green tea supplements appear to be relevant in overweight subjects diagnosed with diabetes, as the intake of green tea extracts has been shown to help with body weight management, characterized by a significant reduction in the body weight, body mass index, and body fat (Asbaghi, et al.) [114]. Additionally, green tea supplementation improved lipid profile by reducing serum triglycerides and total cholesterol (Asbaghi, et al.), followed by a decrease of inflammation markers, such as circulating levels of C-reactive protein, without affecting the malondialdehyde and total antioxidant capacity (Asbaghi, et al.) [115,116]. Finally, green tea also had a beneficial impact on adiponectin, a key hormone mediating metabolic processes responsible for insulin sensitizing and anti-inflammatory effects, and green tea supplementation increased the adiponectin concentrations in patients with type 2 diabetes (Asbaghi, et al.) [117].

Nevertheless, a recent systematic review and meta-analysis of a randomized controlled trial investigating the effect of the supplementary intake of green tea in patients with type 2 diabetes concluded that an additional supplementation of green tea has no significant effect on fasting plasma glucose, fasting insulin, HbA1c, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in this patient group (Asbaghi, et al.) [118] thereby suggesting the need for further clinical trials to establish the anti-diabetic effects of green tea.

Obesity and metabolic syndrome

Obesity, defined as excessive body weight, has become one of the most critical public health problems affecting more than 650 million adults worldwide. Owing that being overweight increases the risk of progression obesity as well as the development of other metabolic health conditions, such type 2 diabetes mellitus, cardiovascular diseases, depression, as well as cancer, implementing appropriate lifestyle modifications (dietary habits, physical activity, sleep etc.) is considered as the most promising strategy in reducing body weight, ultimately leading to a reduced rate of obesity (Wadden, et al.) [119]. Among various dietary approaches to lose weight, dietary supplements of natural origin received significant attention due to their wide accessibility to consumers. Among such supplements, preparations made of polyphenols, including those extracted from tea, may be promising. For example, green tea catechins have been shown to have potential benefits for weight management, linked to their ability to reduce appetite, stimulate thermogenesis and increase energy expenditure. Furthermore, green tea being a source of caffeine, may additionally boost energy levels through the day, leading to increased physical activity and consequently burning extra calories. Interestingly, the synergistic role of both catechins and caffeine from green was confirmed by controlled intervention trials, which demonstrated that ingestion of green tea catechins (270 mg to 1200 mg/day) decreased the heavyweight of the body and also fat accumulation in the body (Rondanelli, et al., Rains, et al.) [120,121]. Experimental studies have confirmed the protective role of green tea against negative effects of a high calorie diet, obesity as well as other metabolic syndromes, thereby indicating that regular consumption of green tea can reduce high fat diet induced obesity in mice models (Lee, et al.) [122]. In particularly, EGCG from green tea inhibits metabolic syndrome, obesity and fatty liver in obese mice (Li, et al., Bose, et al.) followed by additional improvements in the lipid profile, resultant in almost 30% cellular cholesterol level reduction (Maiti, et al.) [123-125]. Also, results of a clinical trial conducted in the group of individuals with metabolic syndrome, whom were given a low energy rich in green tea extract (1 g/day; 890 mg total catechins) confection snack food, after 28 days, demonstrated a positive effect of green tea catechins on intestinal physiology, characterized by alleviation of gut barrier dysfunction in relation to endotoxemia associated low-grade inflammation (Hodges, et al.) [126].

The evidence confirming the effectiveness of green tea preparations in reducing body weight and fat is intensively researched, and so far, studies have demonstrated that green tea supplementation can significantly improve body composition and help in body weight reduction. A systematic review and dose dependent analysis evaluating the efficacy of green tea intake in obese subject have shown that green tea supplementation can reduce body weight (WMD: −1.78 kg, 95% CI: −2.80, −0.75, p=.001) and the Body Mass Index (BMI) (WMD: −0.65 kg/m^2, 95% CI:−1.04, −0.25, p=.001).

Interestingly, participants receiving doses of green tea ≥ 800 mg/day may benefit from significant reduction in Waist Circumference (WC) (WMD: −2.06 cm) and with a treatment duration <12 weeks (WMD: −2.39 cm). The dose response evaluation indicated that green tea may alter body weight, with a more significant reduction when the green tea dosage was <500 mg/day and the treatment duration was 12 weeks. Consequently, this analysis supports the use of green tea for the improvement of obesity indices, which can be highly efficient if combined with a balanced and healthy diet and regular physical exercise in the obese patients (Lin, et al.) [127]. For example, overweight and obese females, who participated in the 8 week long trial, involving a combination of resistance training and a supplementation of green tea polyphenols, increased resting metabolic rate, promoted formation of lean body mass and increased muscle strength, while decreasing body fat, triglycerides concentration in the blood and reduced measure of waist circumference, compared to group which also underwent the exercise plan, however, instead of a green tea supplement, obtained a placebo (Cardoso, et al.) [128]. A clinical trial assessing the effect of co-supplementation with polyphenols, EGCG and Resveratrol (RES) (EGCG+RES, 282 and 80 mg/day, respectively) or placebo in a group of 37 overweight and obese men and women, after 12 weeks, significantly decreased *Bacteroidetes* abundance and tended to reduce *Faecalibacterium prausnitzii* in males but not in females. Interestingly, baseline *Bacteroidetes* abundance was predictive for the EGCG+RES induced increase in fat oxidation in men but not in females. Other bacterial genera and species were not affected by EGCG +RES supplementation, which, all together, may suggest the positive influence of polyphenols' on gut microbiota composition, that promote fat oxidation in the sex dependent fashion (Most, et al.) [129].

In addition, evidence obtained from human trials also confirmed the benefits of green tea on metabolic health management in overweight and obese subjects. Results of a meta-analysis reviewing 16 controlled trials with a total number of 1090 subjects have demonstrated benefits of green tea in reducing BMI (SMD, −0.27; 95% CI, −0.40 to −0.15, P<0.0001) and blood glucose (SMD, −0.22; 95% CI, −0.34 to −0.10, P=0.0003), while HDL cholesterol (SMD, 0.18; 95% CI, 0.01 to 0.35, P=0.03). Nevertheless, this study failed to confirm any significant effect of green tea beverage on blood pressure and other anthropometric, cholesterol and biochemistry outcomes. These results may overall suggest that introducing regular consumption of tea extracts may benefit obese individuals who developed metabolic syndrome symptoms, and ultimately facilitate gradual weight loss and improve glucose and lipid profile (Li, et al.). Similarly, another meta-analysis found that green tea, by favourably acting on BMI value, may have protective effects against the development of diabetes; however only in individuals who have a BMI value of at least 28 or higher (Liu, et al.). Consistently, adding a green tea supplement to the diet of individuals with excessive body weight, with BMI being equal or higher than 28, may help in reducing adverse symptoms of metabolic syndrome, possibly preventing the progression to diabetes (Liu, et al.) [130-132]. For example, for overweight females, aged between 40 and 65 years of age, the dietary supplementation with green plant membranes (5 g) or placebo, once daily before breakfast, after 12 weeks resulted in the significant reduction in the body weight, followed by the further improvements in the lipid profile, demonstrated by reduction of total and LDL cholesterol, when compared to the placebo. Furthermore, females who received green tea supplements reported an increased postprandial release of Glucagon Like Peptide 1 (GLP-1) and decreased urge for the consumption of sweets and chocolate containing foods, compared to the control group (Montelius, et al.) [133].

Cardiovascular Health (CVD)

Cardiovascular Disease (CVD) is the leading cause of death worldwide which, based on WHO estimates, in 2019 affected 17 million individuals, who died predominantly due to heart attacks and strokes (WHO) [134]. Despite significant improvement in cardiovascular care, the occurrence of CVD is expected to rise, along with an increasing prevalence of other cardio-metabolic conditions, including type 2 diabetes and obesity (Belardo, et al.) [135].

To date, many risk factors have been implicated in CVD, with lifestyle habits, including a poor quality diet and sedentary lifestyle, being a major contributor to the cumulative morbidity of CVD (Belardo, et al.) [136]. Similarly to other metabolic conditions, the implementation of dietary interventions aiming to improve overall diet quality appears to be one of the most effective strategies in the management of certain CVD risk factors, including hyperlipidemia, hypertension, hyperglycemia and excessive body weight, ultimately leading to more effective prevention against CVD. As part of dietary habits which can be effective in CVD prevention, certain dietary supplements of natural origin have been suggested, including green tea polyphenols.

Epidemiological studies have shown that daily intake of green tea containing 200–300 mg of EGCG has a beneficial effect on cardiovascular health. For example, in a cohort study, regular intakes of green tea beverage helped to decrease the mortality of CVD. Interestingly, each cup of tea consumed in a day, even accounting for the fact that black tea has less antioxidants than green tea, was associated with an additional 4% lower risk of cardiovascular mortality and a 2% lower risk of occurrence of cardiovascular events, including 4% lower risk of stroke (Chung, et al.) [137]. Furthermore, the regular intake of either black or green tea for at least 3 months, has been shown to efficiently reduce systolic and diastolic blood pressure (by about -3.53 and -0.99 mmHg). In China, green tea consumption has been found to be associated with a reduced risk of mortality from all CVDs, with an increase of one cup of green tea per day linearly decreasing the risk by 5%. An increase in the intake of tea by three cups daily was associated with a decrease in the risk of cardiac death by 26% (Tang, et al.) [138]. In comparison with low or no tea consumption, high intake of green tea has been reported to be related to a decrease in the risk of CVD, coronary artery disease (Zhang, et al.), myocardial infarction and stroke (Pang, et al.) [139,140].

The reduction of CVD risk associated with tea consumption has been attributed to the high concentrations of polyphenols, in

particular flavonoids, found in the green tea beverages, in particularly favan-3-ols, which may help in maintaining adequate vascular function by enhancing the formation of Nitric Oxide (NO). Besides flavan-3-ols, some other tea components, such as quercetin and L-theanine also have been proposed to decrease blood pressure, oxidative status, and damage in animal models of hypertension (da Silva Pinto). Experimental studies have confirmed the ability of tea-derived to favourably modulate enzymes involved in oxidative stress, anti-inflammatory properties, as well as their capability to improve endothelial function and enhance nitric oxide status. Consequently, the cardioprotective properties of green tea may be mediated by multiple mechanisms, not limited to inhibitory effects on oxidation, vascular inflammation and thrombogenesis. Catechins may also provide antihypertensive benefits that can decrease the production of pro-inflammatory cytokines and platelet aggregation, leading to the overall improvement of endothelial dysfunction. Although most preclinical studies conducted on animal models of hypertension have found that the administration of tea can reduce elevated blood pressure, decrease the formation of vascular reactive oxygen species, and improve endothelium-dependent relaxation in the aorta; results obtained from human interventions remain inconsistent. For example, results of a meta-analysis conducted on randomised clinical trials failed to demonstrate any effects of short term intake of green or black tea on systolic or diastolic blood pressure, while the long-term tea consumption for at least 12 weeks lead to reduced mean systolic and diastolic blood pressure by 1.8 and 1.4 mmHg, respectively (Liu, et al.). Interestingly, supplementation with green tea extracts has been found to inhibit the intestinal absorption of lipids and to up regulate LDL receptors in the liver, which leads to improved blood lipid profiles. In terms of the effects of green tea consumption on the risk of stroke, a recent meta-analysis conducted on cohort studies, indicated a significant association between the highest green tea consumption and reduced risk of stroke (summary RR: 0.74; 95% CI, 0.66-0.83). Furthermore, the dose response analysis found a nonlinear association between green tea consumption and the risk of stroke. Interestingly, compared with non-consumers, the RRs (95% CI) of stroke across levels of green tea consumption were 0.91 (0.89–0.94) for 150 mL/d, 0.84 (0.80–0.89) for 300 mL/d, 0.79 (0.74–0.84) for 500 mL/d, 0.77 (0.72–0.82) for 900 mL/d, and 0.84 (0.77–0.91) for 1500 mL/d; thereby suggesting that green tea intake is inversely associated with the risk of stroke, especially among those with moderate consumption (Wang, et al.).

Green tea and mental health

Mental health, defined by WHO as a state of well-being in which the individual realizes his or her own abilities can cope with the normal stresses of life, can work productively and fruitfully, and is able to make meaningful contribution to his or her community" (WHO), represents an individual ability to adapt to environmental stressors and is reflected in their thoughts, emotions, and behaviours, which can be shaped by factors such as age, local and cultural norms, and expectations. The prevalence of mental health problems is increasing worldwide due to a combination of genetic, environmental, and psychological factors that can significantly impact human behaviour and daily functioning. Although various mental conditions can differ widely in their course and symptoms, they may compromise the quality of life of those affected despite pharmacologic treatments and psychotherapy. As a result, there is a growing interest in additional self-help strategies, such as the consumption of plant bio-active rich foods that may aid in the prevention and management of mental illnesses, addressing the root causes of mental health problems and complementing traditional treatments.

Therefore, use of dietary polyphenols, such as tea derived bio-actives, may be advantageous in the prevention and treatment of several chronic disorders, owing to their ability to counteract inflammation, oxidative stress, and neurodegeneration. Polyphenols may positively impact brain health not only be interacting directly with brain cells, but also by modulating the communication between the gut brain axis. These effects were supported by a series of preclinical studies that have so far demonstrated that polyphenols have the potential to benefit individuals with a range of brain diseases, including both neurodevelopmental (e.g., Down's syndrome and autism spectrum disorder) and neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease), as well as psychiatric disorders (e.g., depression and anxiety).

Although tea polyphenols may be considered promising nutraceuticals for psychiatry practice, the impact of these compounds on the gut brain connection must be further explored (Serra, et al.). As the major pathologic mechanism of depression includes the dysregulation of the HPA axis, impairment of the neurotransmitter metabolism and low microbiome diversity of the gut brain axis, followed by increased oxidative damage and ongoing systemic inflammation, tea compounds appear to be beneficial, as to date studies have indicated their ability to restore HPA axis reactivity by dramatically lowering high plasma corticosterone (stress hormone) as well as adrenocorticotropin concentrations. Moreover, green tea may have an antidepressant effect which is thought to be achieved by increasing the concentrations of hormones and monoamine neurotransmitters that control mood and motivation, including dopamine, norepinephrine, and serotonin. Lastly, green tea polyphenols, having a high antioxidant capability, may protect against neurodegeneration resulting from progressive ageing and inefficient free radical neutralisation (Bag, et al.).

DISCUSSION

The bioactive compounds extracted from green tea have been found to offer significant protection against the harmful effects of free radicals and oxidative damage. This has been demonstrated through their ability to act as a defence mechanism against lipid peroxidation products in various organs, including the brain as shown through *in vivo* studies. Experimental studies found that green tea intake can reduce the activity of potent pro-oxidant enzymes, like superoxide dismutase and glutathione peroxidase, while at the same time promoting antioxidant defences attributed to glutathione reductase and catalase in the brain. In hypoxic conditions, green tea catechins have been shown to prevent microglial cell death

through suppression of the hypoxia/reperfusion activated autophagy in the brain structures (Bag, et al.).

Moreover, the bio-active components of green tea extracts are efficiently utilised by microbial communities in the gut and used to produce microbial derived metabolites, whose beneficial effects have been demonstrated in stress management, anxiety reduction and prevention against depression in high risk populations. These beneficial effects are attributed to bioactive compounds found in tea beverages, for instance caffeine, flavan-3-ols, and L-theanine. In particular flavan-3-ols, such as EGCG and (−)-epicatechin, that upon digestion have been shown to possess the ability to penetrate the Blood-brain barrier, and ultimately act on the neural signaling pathways in brain structures (Bag, et al.). In addition, caffeine and L-theanine together demonstrated a great effect on excitatory or relaxing functions and exposure to equivalent molar concentration of L-theanine can antagonise action of caffeine (da Silva Pinto). Interestingly, the ingestion of L-theanine from green tea has been shown to not only reduce behavioural depression and cognitive dysfunction, but also enhance the lifespan of animals which were exposed to psychosocial tension (Unno, et al.).

Epidemiological studies have found that there is an association between tea intake and a lower incidence of depression, with regular tea drinkers being less likely to suffer from depression compared to non- or occasional tea drinkers (Hintikka, et al.). A recent study conducted on the demographic and dietary data from 1572 adults living in southern Italy showed that individuals with a moderate intake (up to 1 cup/glass per day) of tea (or coffee) were less likely to have high perceived stress (OR=0.61, 95% CI: 0.45–0.84) and depressive symptoms (OR=0.56, 95% CI: 0.39–0.80) (Micek, et al.). Similarly, the frequent intake of green tea decreased the prevalence of depressive symptoms in the older Japanese population (da Silva Pinto). In a cross sectional study conducted on the group of elderly Japanese participants diagnosed with depression, green tea consumption was found to be independently correlated with the reduction of depressive symptoms. Interestingly, those who drank 2-3 cups of green tea a day expressed 4% less symptoms than those who drank 1 cup or less; those who drank 4 cups or more expressed 44% less depressive symptoms (Niu, et al.). In another clinical study involving 74 healthy participants, the consumption of green tea for five weeks was effective in reducing depressive scores compared with the placebo group, implicating the potential role of green tea bio-actives in increasing reward learning (Zhang, et al.). Dietary intervention with decaffeinated green tea (6 cups/day) after 6 weeks significantly improved depression, anxiety, stress and mental health consequences associated with stuttering in adolescents aged between 12 and 18 years old. In addition, an increased consumption of green tea significantly reduced elevated levels of adrenal stress hormones, including cortisol, dehydroepiandrosterone, acetylcholine and corticosterone, and increased the cortisol: dehydroepiandrosterone ratio in the stuttered adolescents, as well as in the control group, thereby suggesting that regular consumption of decaffeinated green tea beverage enriched in catechins (1,580 mg) and other related polyphenols improved mental health in younger aged individuals (Almudhi and Gabr). Although several potential therapeutic mechanisms of dietary polyphenols towards establishing cognitive resilience to neuropsychiatric disorders have been established, only a handful of studies have systematically identified how the interaction of the gut microbiota with dietary polyphenols can synergistically alleviate the biological signatures of depression. Therefore, combining polyphenols with probiotics may provide a novel therapeutic strategy for depression that may have the potential to alleviate neuroinflammation, reduce oxidative stress and balance serotonin metabolism, simultaneously targeting several of the major pathological risk factors of mood disorders (Westfall and Pasinetti).

Green tea has been proposed to have a protective role against neurological and cognitive dysfunction, especially in the elderly (Conger and Singg). A pilot study, conducted on a group of Japanese elderly participants, with a supplementation of 2 g of green tea powder for 3 months, significantly improved the score of the participants on the mini mental state examination, suggesting that green tea supplementation might improve cognitive functioning (Ide, et al.). Similar effects were also observed in an epidemiological study that examined the relationship between green tea consumption and incidence of dementia in 13,645 elderly Japanese participants over 5.7 years. The results of this study found that those who drank 5 cups of tea or more developed dementia 27% less often than those who drank less than 1 cup per day (Tomata, et al.). A systematic review assessing the effects of green tea or green tea extracts rich in L-theanine and epigallocatechin gallate on general neuropsychology, cognition and brain functions in humans supported green tea benefits on psychopathological symptoms (e.g. reduction of anxiety), cognition (e.g. benefits in memory and attention) and brain function (e.g. activation of working memory), following the habitual daily consumption of at least 100 ml per day. However, the review highlighted that these effects cannot be exclusively attributed to a single constituent of the beverage. This is exemplified in the finding that beneficial green tea effects on cognition are observed under the combined influence of both caffeine and L-theanine, whereas separate administration of either substance was found to have a lesser impact (Mancini, et al.). A later review, systematically examining the association between green tea intake and dementia, Alzheimer's disease, mild cognitive impairment or cognitive impairment by using the cross sectional and cohort observational studies, found that the regular intake of green tea might reduce the risk for dementia, Alzheimer's disease, mild cognitive impairment or cognitive impairment in free living population. The authors proposed mechanisms of these effects, which were attributed to the high antioxidant capacity of green tea catechins, which acting as powerful free radical scavengers, can help reduce oxidative stress. Furthermore, anti-inflammatory effects of tea bio-actives may help to reduce brain inflammation, which has been implicated in dementia. Finally, neuroprotective properties of the main catechin, EGCG, may inhibit beta-amyloid formation and its aggregation in brain structures (Kakutani, et al.). The benefit from drinking green tea was also reported for people with down syndrome in a study of 29 young adults with Down Syndrome, who given a EGCG supplementation, had higher accuracy in visual memory recognition and spatial working memory tasks, as well as

improved quality of life and social functioning demonstrated as better behavioural control when compared to the placebo (de la Torre, et al.).

Similarly, intake of green tea bioactive L-theanine increases the anti-stress effects by the suppression of cortical neuron excitation, thereby leading to reduced psychological and physiological stress (da Silva Pinto). Series of clinical trials focusing on L-theanine supplementation from green tea extracts confirmed its benefits for stress and anxiety management. For anxiety, results of a systematic review assessing the green tea amino acid, L-theanine, support its benefits for mental wellbeing, including improvements in mood, cognition and a reduction of stress and anxiety-like symptoms, thereby suggesting that the supplementation of 200–400 mg a day of L-theanine may help in the reduction of stress and anxiety in people exposed to stressful conditions (Williams, et al.). A short-term intervention with L-theanine doses of 200 mg/day reduced subjective anxiety and lowered the total Hamilton Anxiety Rating Scale (HARS) score in comparison with Alprazolam and placebo on the 'Troubled' subscale of the Visual Analogue Mood Scale (VAMS), however with no significant effects on the State Trait Anxiety Inventory (STAI) and Beck Anxiety Inventory (BAI) scores in the healthy participants (Lu, et al.). A similar dose of L-theanine (200 mg) given to healthy university students with high and low anxiety propensities resulted in a decrease in HR and an improved reaction time response among high anxiety propensity participants compared to the placebo. The STAI results indicated time dependent decrement patterns of anxiety, however, no differences were observed between groups, potentially attributing to the participants being familiar with the testing environment (Higashiyama, et al.). In the long term, an eight-week phase II randomized clinical trial conducted in patients with generalized anxiety disorder, treatment with doses of 225 mg L-theanine twice daily failed to improve symptoms compared with the placebo (Sarris, et al.). In relation to stress response, several studies found beneficial effects of L-theanine. For example, the supplementation with either L-theanine (200 mg), caffeine (100 mg) or a placebo, significantly lowered systolic and diastolic blood pressure in response to the mental tasks, but not the cold exposure compared to the placebo. These effects were not observed in the 'low response' group (Yoto, et al.). Results of a study examining the effects of L-theanine (400 mg/day) given to pharmacy students during a highly stressful period for 17 days, found that the SAA was higher in the placebo group, while the L-theanine group maintained the baseline observed during the routine activities at the university. Interestingly, the STAI values were not different between the two groups, however, the psychosocial stress was lower in students receiving L-theanine supplementation compared to the placebo (Unno, et al.). A crossover trial investigated the anti-stress effects of L-theanine (200 mg) administered in the form of a nutrient beverage commercially available (NeuroBliss®) *vs.* the placebo in a group of 34 healthy volunteers was associated with a decrease in subjective stress responses and reduced self-rated stress response measured 1 h post-administration. There were no significant differences in the subjective stress response 3 h after consumption; however, salivary cortisol levels were significantly lower in the L-theanine group in comparison to the placebo after this time (White, et al.). The shanghai brain aging study examined the association between tea consumption and performance on assessment tasks related to the cognitive function, episodic memory and executive function in cognitively healthy older adults and older adults with mild cognitive impairment in a total sample of 1849 participants with a mean age of 69.5 years of age. The study revealed a significant relationship between tea consumption and measures of episodic memory exclusively in cognitively healthy individuals, but not in those with mild cognitive impairment (Xu, et al.).

CONCLUSION

To date, there are a growing number of studies supporting the health benefits associated with regular consumption of polyphenol rich foods and beverages, including tea. Green tea, in particular, is abundant in various phytochemicals, including catechins, which have been shown to possess anti-tumor, anti-inflammatory, anti-diabetes, anti-obesity, anti-hypertension, anti-aging, anti-viral, and antibacterial properties. While several mechanisms have been proposed to explain the effects of green tea polyphenols, emerging research suggests that bio-actives from green tea may exhibit prebiotic effects and modulate the gut microbiota composition, promoting the production of health-promoting bio-actives such as SCFA. Therefore, incorporating green tea into one's daily diet may promote good cardio-metabolic and mental health and prevent the development of chronic diseases such as depression, obesity, diabetes, and CVD. However, despite promising findings, a limited number of studies and inconsistencies in observations calls for further research to confirm the utility of green tea and its bio-actives in public health.

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