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Natural Polyphenols: Potential for Disease Prevention

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Abstract

Natural plant remedies have been used for thousands of years to offer prevention, relief and cure for all types of illnesses, and people in the ancient times believed that good and sufficient food was vital for the body survival, to perform better and deter various diseases. Epidemiological studies suggest that diets high in polyphenols may have a protective effect against oxidative stress and play a critical role in the prevention of some common diseases such as hypertension, diabetes and obesity. However, the diversity and complexity of these compounds implies that much remains to be elucidated concerning the mechanisms by which these compounds influence health. We have recently reported that dark chocolate (Barry Callebout, Belgium) and pomegranate juice or extract consumption can reduce fasting blood glucose levels, insulin resistance, systolic and diastolic blood pressure. The effects of green coffee bean extract, green tea and grape juice on blood pressure and glucocorticoids were also investigated and compared in healthy volunteers of different age, gender and BMI. There is now growing evidence that polyphenols supplements and food rich in polyphenols may play a critical role in the prevention of several contemporary diseases such as obesity and cancer. I suggest that it is absolutely vital to realize that the intake of polyphenols-rich foods has to be considered as protective measure against the development of the epidemic of chronic diseases rather than a cure, at least for the present time. Therefore, changing the dietary habits and culture has to start at an earlier stage in life, particularly in the UK and Europe. In conclusion, over the last few decades, there has been tremendous surge of attention in the action of natural polyphenols and their effects on various body functions and metabolic processes. However despite the huge increased research throughout the world and interest by the public, the majority of the health benefits and physiological activities attributed to nutrients and food products require further research to elucidate the mechanism/s of action, and side effects.

Keywords: *Polyphenols; Antioxidants; Oxidative stress; Prevention; Diabetes; Cardiovascular; Obesity; Cancer*

Introduction

Plant-based natural remedies have been known to offer relief and cure since ancient times, and for many centuries, people have associated good health with adequate and nutritious food, and believed in the power of food constituents to prevent or cure diseases [1-3]. For example, the protective effects of tea against cardiovascular disease and coffee against type 2 diabetes. In the last decade, scientific and commercial interest in polyphenols has grown dramatically, and thousands of studies investigating their bioactivities, metabolism and health effects are published every year. However, there is still a lot of info lacking as far as the mechanism of action of these molecules [4] and what happens to them inside the body. Dietary antioxidants are referred to as non-enzymatic antioxidants and include polyphenols, carotenoids, flavonoids, phenolic acids, vitamins, minerals and organosulfur compounds. In comparison, enzyme cofactors, enzymes and low molecular weight molecules are recognised as endogenously produced antioxidants [5]. Nowadays, as a consequence of the extensive quantity of environmental factors that contribute to the excessive formation of reactive oxygen or nitrogen species (RONS), as well as the inadequacy of the body's endogenous defence system, oxidative damage can easily accumulate if dietary antioxidants are absent [6]. Under standard circumstances, RONS can be removed by antioxidant enzymes including catalase, superoxide dismutase and glutathione peroxidase. Nevertheless, during periods of diminished levels of enzymatic antioxidants, often as a consequence of CVD, ageing or excessive production of free radicals, increasing dietary antioxidant consumption is fundamental so that the RONS balance is restored [7].

Various dietary antioxidant compounds play a vital role as free radical scavengers and protect the body from oxidative damage by preventing the free radical mediated process and lipid peroxidation; in order to do so, polyphenol antioxidants can hinder chain reactions or act as a preventative measure [8,9]. Several molecules have been extensively researched for their mechanistic effect and health benefits such as resveratrol, epicatechins, quercetins, ellagitannins and anthocyanins. In this reflective mini review, I try to discuss briefly some of the data available so far to support the notion of increased health benefits following the consumption of polyphenols rich food and supplements, and what are the challenges that will be encountered trying to elucidate the mechanism of actions and potential use of polyphenols for the prevention of disease?, and what about the importance of bioavailability of these compounds and their metabolites.

Epidemiological, *in vivo, in vitro* studies and clinical trials have now associated plant-based diet intake (especially rich in Polyphenols) with various beneficial biological activities that can ameliorate chronic disease risk factors such as diabetes type 2, CVD, obesity, neurodegenerative disorders and some types of cancer [10-15]. Polyphenols are a group of natural compounds characterized by the presence of several hydroxyl groups on an aromatic ring [16]. Their importance stems from their abundance in the diet, their antioxidant properties and ability to regulate various biological/biochemical processes perhaps through a number of cellular signaling pathways and modulation of genes expression [17-19]. The rise of polyphenols and in particular, flavonoids potential to protect against oxidative stress linked to a host of diseases such as obesity, hypertension, childhood cancer, dyslipidemia, memory and cognitive dysfunction has seen a huge increase in the market of functional antioxidants.

Food (polyphenols in particular) has become essential not only for energy production and body matter of classic metabolism, but also a conditioning environment that modulates the epigenome activity and influences stress adaptive responses, energy metabolism, immune homeostasis, and the physiology of the body [20,21]. It can be postulated that the pleiotropic effects of plant phytochemicals on body systems can be translated into stable epigenetic patterns of gene expression, and thus diet interventions designed for healthy aging might become a hot topic in nutritional epigenomic research [22].

We have investigated the health benefits of a variety of food products, fruits and berries juices or extracts in our laboratory such as dark chocolate, pomegranate juice and extract, grapes, green tea and coffees (including their extracts) and purple potato [23-25], and a huge number of plant products and nutrients have been investigated by thousands of researchers all over the world.Nowadays, Research fuelled by consumer demands and industry has concentrated on the therapeutic potential of nutrients that resulted in an explosion of new research topics and industry; Functional foods, Nutrigenomics and proteomics, Nutraceutial and Nutrapharmaceuticals etc. The research and interest were driven by many reasons; among some, the increase in side effects and drug-resistance of current pharmaceuticals, the rising of the epidemic of overweight and obesity world wide, stressful lifestyle, aging population and the surge in metabolic diseases such as diabetes, cancer and CVD that are considered to be the most important cause of mortality. Summary of some of our findings are listed below: Green coffee bean extract (90 mg chlorogenic acid per day) decreased systolic blood pressure from 119.4 ± 10.5 to 113.8 ± 9.1 mmHg ($p = 0.05$). Green tea (4 cups per day) significantly reduced systolic blood pressure by 7.1 mmHg ($p < 0.001$) and diastolic blood pressure by 4.8mmHg over 14 days ($p < 0.01$). A significant reduction in systolic BP following the dark grape juice in the exercisers (from 136 ± 8.7 to 132.2 ± 8.9 mmHg, $p = 0.03$) and the non-exercisers (from 137.7 ± 10.1to 135.2 ± 9.9 mmHg, $p = 0.04$), but the reduction was more marked for the exercisers and Diastolic BP was only significantly reduced in the exercisers group ($p = 0.05$). In addition, green tea consumption reduced mean fasting total cholesterol by 0.556 mmol/L ($p < 0.008$), BMI by 0.34 kg/m^2 ($p < 0.01$), body weight by 0.96 kg ($p < 0.01$) and body fat mass by 2.36% ($p < 0.05$). No changes were detected in BMI or body weight following green coffee bean extract or grape juice. Following green coffee bean extract consumption urinary free cortisol was reduced from 1.0523 to 0.763 ± 0.40 nmol/kg ($p = 0.07$). Free cortisone excretion was increased from 0.712 ± 0.38 to 0.932 ± 0.24 nmol/kg ($p = 0.007$), and the ratio of cortisol/cortisone was reduced (from 1.48 ± 0.65 to 0.82 ± 0.42, $p = 0.03$). Dark grape juice intake by exercisers and sedentary groups indicated that urinary basal antioxidant capacity was found to be significantly lower in the latter compared to exercisers ($p = 0.05$), and that exercisers had a slight but significant increase in antioxidant capacity ($p = 0.05$) and decrease in the lipid peroxidation marker, TBARS (from 31.2 ± 9.12 to 24.4 ± 7.6 µmole/day, $p = 0.028$) following grape juice consumption [26].

No serious side effects were reported following the intake of natural polyphenols. We and others have carried out several studies on pomegranate juice/extract, dark chocolate and green tea intake and observed the majority of volunteers have tolerated these products very well and did not report undesirable effects. However, there was only one subject who reported headache possibly due to unusual big reduction in blood pressure that possibly due to the fact that the subject was on antihypertensive drugs. The following are some possible minor side effects that were reported following the consumption of pomegranate juice, dark chocolate and green tea: Stomach upset and constipation if the product was taken before meal presumably due to the tannins content which increase stomach acid. To rectify this, the subjects were advised to take the polyphenol-rich food or supplement with or following the meals. Caffeine is one of the constituents of green and black tea, and green tea has less caffeine than coffee or black tea. A moderate amount of caffeine is less than 200 mg a day. In some subjects, too much caffeine might cause headache, nervousness, sleep problems, diarrhoea and irregular heart beat. Catechins and tannins could cause a decrease in the absorption of iron from food. Therefore, people suffer from iron-deficiency anaemia; the recommendations are to consume tea and pomegranate products between meals. Lastly, some polyphenols can cause drug interactions with certain medications.

Over the last two decades, polyphenols have been implicated in the prevention of a number of oxidative-related diseases including cancer, cardiovascular disease, hypertension and diabetes. These compounds occur largely in plant and plant-derived products and are extensively involved in plant defence mechanisms. Antioxidant polyphenols intake has been found to reduce risk of chronic diseases, such as coronary heart disease, stroke, type 2 diabetes and some cancers. For this reason, they are now regarded as important components of a healthy diet and are thought to be partly responsible for the health benefits of an increased fruit and vegetable consumption. They may also explain the protective effects of tea against cardiovascular diseases and coffee against type 2 diabetes. In the last decade, scientific and commercial interest in polyphenols has grown dramatically, and thousands of studies investigating their bioactivities, metabolism and health effects are published every year. Research looking into the health benefits of dietary polyphenol intake is still conflicting. This is mainly due to studies showing conclusive results *in vitro* but not *in vivo* [4,27]. As chemical entities, polyphenols have been shown to have antioxidant [28], neuroprotective [29,30], chemo protective [31], anti-inflammatory [32], arthero protective [33] properties and may decrease the risk of cardiovascular disease [34] and type 2 diabetes [10]. In addition, data from epidemiologic studies indicate the presence of an inverse relationship between human disease and dietary polyphenol [35], and recently, a large study investigating the effect of consumption of diet rich in polyphenols [36] reported an inverse association between the consumption of polyphenol-rich foods and the risk of cardiovascular disease or overall mortality.

It has been fairly established that natural polyphenols could act on multiple targets in some metabolic pathways related to carcinogenesis, suppression of certain cancers, tumor cell proliferation and apoptosis [37], metastatic spread, angiogenesis or drug and radiation resistance [38]. Inflammation and oxidative stress are also thought to be important causes of carcinogenesis [39]. Abnormally high levels of free radicals weaken the antioxidant defense mechanism of the body, causing an increase in lipid peroxidation and disturb various cell signaling causing mutations [40]. as well as triggering the production of nuclear factor k-B (NF-kB). NF-kB is a pro-inflammatory control which regulates inflammation and oxidative stress accounting for the detriment in immune function, muscle injury and fatigue [41]. However, the claimed anti-cancer effects of polyphenols are still controversial, since results of correlations between *in vitro* effects and *in vivo* evidence are poorly established. Numerous studies are being published in a variety of journals to describe the mechanism of natural polyphenols anti-cancer activity. Few examples are highlighted in this section. Green tea polyphenols, curcumin and ellagic acid exhibit effective chemopreventive actions against both the initiation and promotion/progression stages of carcinogenesis in addition to their potent antioxidant effects [31,42]. Curcumin was shown to inhibit chemically induced preneoplastic lesions in the breast and colon and neoplastic lesions in the skin, and it can be argued on the basis of the data published that the current state of knowledge on this phytochemical is sufficient to advocate its advancement into phase II clinical studies [43]. Green tea polyphenols were found to exhibit anti-mutagenic activity *in vitro*, and they inhibit carcinogen-induced skin, lung, forestomach, esophagus, and duodenum and colon tumors in rodents. Several mechanisms appear to be responsible for the tumor-inhibitory properties of green tea and curcumin including enhancement of antioxidant status (glutathione peroxidase, catalase and quinone reductase) and phase II (glutathione-S-transferase) enzyme activities; inhibition of chemically induced lipid peroxidation; inhibition of irradiation-and TPA-induced epidermal ornithine decarboxylase and cyclooxygenase activities; inhibition of protein kinase C and cellular proliferation; anti-inflammatory activity; and

enhancement of gap junction intercellular communication. Moreover, researchers have reported possible epigenetic contributions of dietary polyphenols in cancer chemoprevention, and nutritional polyphenols (soy, genistein, resveratrol, catechin, curcumin) are currently being evaluated for their ability to reverse adverse epigenetic marks in cancer cells and potentially attenuate tumor progression, prevent metastasis or increase anti-cancer drug sensitivity [44]. Dietary polyphenols have been implicated in the prevention and treatment of several types of cancer such as the flavonoid quercetin as an adjunct agent for the treatment of leukemia [45], and some subclasses of polyphenols in the prevention and treatment of prostate cancer [46].

Polyphenols or "biophenols" are often categorized into 4 groups depending on the number of phenol rings embodied in their structure and the elements that bind these rings together. Distinction is hence made between phenolic acids, flavonoids, stilbenes and lignans [16,47]. The term "biophenols" is preferred by some researchers as it is a comprehensive and more accurate term that includes all phenolic plant active chemicals [15,48]. So far, thousands of polyphenols have been identified in the diet [49] and the average dietary intake of these plant-products is estimated to be in the range of 1g/day [47,50]. Nevertheless, the maximum plasma concentration of polyphenols rarely exceeds 1μM following ingestion of 10-100 mg of a single phenolic compound [47]. As a consequence only a minority of these compounds are of therapeutic value. In fact, the structural diversity of polyphenols implies differences in bioavailability and subsequent biological activity of these compounds which means that the most abundant polyphenols in the diet are not in effect the most biologically active [16,47]. Therefore, it isimportant to differentiate between the different structures, bioavailability and consequent biological activities of these compounds in order to identify the most relevant polyphenols to health. Bioavailability of the polyphenols has been a controversial and important issue to resolve as most of the evidence for the health benefits of dietary polyphenols were concluded from epidemiological studies [51]. It is paramount now to establish a definition of the bioavailability of the diverse groups of polyphenols, and it seems that the most abundant ones in our diet are not necessarily those that have the best bioavailability profile.

Functional Food Centers were established in USA, UK and other countries to integrate and combine the cutting-edge research expertise in the bio-medical sciences and nutrition with practical business experience in order to develop and commercialize functional foods for alternative prevention and treatment of chronic diseases and other human needs. A new definition of functional foods has been adopted: "Functional Food is a Natural or processed food that contains known biologically-active compounds when defined in quantitative and qualitative amounts provides a clinically proven and documented health benefit, and thus, an important source in the prevention, management and treatment of chronic diseases of the modern age".

It is now widely accepted that natural polyphenols from a variety of sources and foods may play an important role in the prevention of cancer, cardiovascular disease and cognitive function, obesity, diabetes type 2 and Alzheimer's Disease [11,16,52-54]. During the last decade, our group has conducted research projects on a variety of functional foods including the polyphenolic antioxidants. Fruit juices (pomegranate, dark grape), green tea, green coffee and its extract, dark chocolate, and liquorice were investigated. Effects on body composition, BMI, blood pressure, insulin and insulin resistance, glucose, steroid hormones (Cortisol, Cortisone and Testosterone), lipids and lipoproteins have been reported. For example, pomegranate pure juice intake was found to reduce insulin resistance, blood pressure and also inhibit the enzyme responsible for activating the stress hormone, cortisol thereby reducing its levels at the target tissues [10]. This discovery is of particular importance, not only in reducing the chronic stress levels, but also in the fight against serious diseases such as obesity, type 2 diabetes, CVD and metabolic syndrome [55-57] since the expression of this enzyme was found to be increased in adipose tissues. Liquorice intake was found to influence many steroid hormones synthesis and metabolism [58]. As we all know that steroid hormones regulate and maintain a number of biological functions in the body, and my hypothesis is that it would be very important to investigate any associations between the effect of polyphenols and steroid hormones in order to pin point their mechanism of action and to suggest possible explanations for their health benefits.

Polyphenol-rich chocolate may now be included in the diet of individuals with type 2 diabetes as part of a balanced approach to diet and lifestyle, with a potential reduction in cardiovascular risk without detrimental effects on weight or glycemic control [10,59,60]. A number of studies have demonstrated that moderate dark chocolate consumption may exert protective effects against the development

of type 2 DM risk factors and cardiovascular disease. Several mechanisms have been proposed to explain this positive influence notonly on insulin sensitivity and vascular endothelial function but also metabolic (fat and carbohydrate), anti-hypertensive, anti-thrombotic, and anti-inflammatory effects, including changes in oxidant defense mechanisms, cytokine production, and platelet function. Nevertheless, due to several limitations ofthe data available, future studies should provide information about type of chocolate used, its polyphenols content, especially flavanols, and the flavanol plasma levels achieved. Furthermore, they haveto consider other potentially active substances present in cocoa (e.g., potassium, magnesium, and theobromine). Mellor., *et al*. [61] reported an improvement in atherosclerotic cholesterol profile in these patients by increasing HDL cholesterol and improving the cholesterol/HDL ratio following chocolate intake. However, caution must be considered when recommending cocoa or chocolate to such patients who tend to be obese. Evidence suggesting a potential role of diet in regulating glucocorticoid metabolism and the ability of polyphenols to both adversely and positively affect cortisol metabolism, investigating the effect of chocolate polyphenols on cortisol metabolism in overweight and obese individuals, and assessing association between cortisol, glucose, insulin, and blood pressure and lipid profile might be essential in elucidating the mechanisms by which these phenolic compounds influence the above metabolic parameters. It has also been observed that the hypotensive effect of cocoa might be mediated through increasing nitric oxide levels. Cocoa flavonols have been shown to increase nitric oxide production by cultured human vascular endothelial cells and improve endothelium-dependent vaso relaxation in brachial arteries of healthy humans [62]. The renin-angiotensin-aldosterone system is known to be animportant regulator of blood pressure homeostasis. *In vivo* inhibition of angiotensin converting enzyme in humans following ingestion of polyphenol-rich pomegranate juice has been reported, providing further evidence for the need to investigate potential modulation of angiotensin converting enzyme activity by polyphenols.

The mechanisms for the biological actions of natural polyphenols have been mainly attributed to their antioxidant properties; however, during the last decade, extensive research has led to a new consensus and realization that these nutritional foods and products may exert their function through multiple mode of actions (pleiotropic effects) affecting various cellular pathways. For example, the inhibitory activity of pomegranate, tea and green coffee on the enzyme 11βHSD1 which activates the stress hormone, cortisone to cortisol as discussed in this review and recently published [24,63,64]. The inhibitory mechanism of polyphenols on several enzyme systems have been widely reported; one interesting and important example is the effects of tea catechins on glucuronidation of toxins (i.e. conjugation with glucuronate which is especially important due to the large number of drugs and chemical carcinogens that are detoxified through this pathway). Révész., *et al*. [65] have reported that epigallocatechin gallate and other green tea polyphenols inhibited glucuronide transport across the endoplasmic reticulum membrane by inhibiting both β-glucuronidase activity and glucuronide transport in native vesicles of rat liver microsomes, and concluded that this action might potentially contribute to the cancer-preventing effect attributed to these dietary catechins. On the other hand and paradoxically, green tea was reported to enhance the deglucuronidation of testosterone by inhibiting UDP-glucuronosyltransferase (UGT2B17) enzyme using an *in vitro* assay, and therefore, it could be postulated that tea catechins can prolong the half life of testosterone in blood and delaying its metabolism and excretion through the inhibition of glucuronidation [66]. These opposite and diverse effects require to be further investigated. Maraldi., *et al*. (2014) have published an interesting article reviewing a multitude of dietary polyphenols and their effects on cell biochemistry and pathophysiology. The pleiotropic effects of these polyphenols were evident as to their role in redox modulation and inflammatory processes, molecular signaling, stem cell proliferation and differentiation, metabolism regulation, potential effect in cancer and neurodegenerative diseases in addition to their known protective effects in lowering cardiovascular disease risk factors and blood pressure through their antioxidant properties and affecting endothelial nitric oxide synthase and thereby modulating nitric oxide bioavailability [23,67]. Nowadays, a huge number of studies have investigated other mechanisms of action of polyphenols and found that the biological actions of EGCG are mediated by specific mechanisms other than its well-known anti-oxidant properties [68]. They reported that EGCG can directly interacts with cell surface membrane proteins and specific known receptors, and that treatment of cells with EGCG regulates specific intracellular signaling pathways and transcription. Natural polyphenols found to also have potent anti-allergic activities that have been shown in different disease models and in human clinical trials [69]. The authors have reviewed the role of flavones, flavone-3-ols, catechins, anthocyanidins, flavanones, procyanidins, and resveratrol in improving the disturbed Th1/Th2 balance and suppressing antigen-specific IgE antibody formation.

I think it is absolutely vital to realize that the intake of polyphenols-rich foods has to be considered as protective measure against the development of the epidemic of chronic diseases rather than a cure, at least for the present time. Therefore, changing the dietary habits and culture has to start at an earlier stage in life, particularly in the UK and Europe. In fact, the habitual intake of flavonoids in Europe is below the amount reported to exert a significant health benefit that could be due to the lack of flavonoid intake data in the general population [52,70].

Conclusions

Over the last few decades, there has been tremendous surge of attention in the action of natural polyphenols and their effects on various body functions and metabolic processes. However despite the huge increased research throughout the world and interest by the public, the majority of the health benefits and physiological activities attributed to nutrients and food products require further research to elucidate the mechanism/s of action, and side effects if any. There is in fact a paucity of data on safety of natural products. Adverse effects were not clearly reported but they range from hypotension and gastrointestinal symptoms to anemia. The average intake of flavonoids in Europe is estimated to be lower than the amounts that were thought to produce unwanted effects. As far as the public, there will be greater demand for nutraceutical polyphenols intake in the hope of preventing or curing chronic diseases and this has to be encouraged. In addition, there will be more pressure on scientists in order to develop fuller understanding of the mode of action of polyphenols. Clinicians and pharmacologists will always prefer to use single molecule therapeutic pharmaceutical drugs. However, it will be more likely difficult to apply this approach for natural products because the effects of plant extracts and natural polyphenols are mediated possibly through a naturally formulated, multi-mechanistic mode and in a synergistic way. Therefore, the task of elucidating the mechanism of action of these products will be far harder.

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