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Polyphenols: novel applications in human health

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Abstract

The diverse actions of polyphenols on human metabolism are only beginning to be understood. Although the actual cellular targets of polyphenols remain speculative, there is growing appreciation of their actions on gene expression, gut health, and control of mitochondrial quality and function. This paper reviews some of these newer potential targets of polyphenols, and outlines the levels of polyphenols required to activate such potential targets.

Introduction

Polyphenols represent a complex group of phytochemicals that provide one of the main methods that plants use to defend themselves from pathogens, predators, and environmental stresses. They are also nutrients that can have a potentially profound effect on human health by changing genetic expression, maintaining gut health, and controlling mitochondrial function.

There are more than 8,000 known polyphenols, and probably twice that number that have not been structurally analyzed. Little was known about the biological activities of polyphenols before 1995[1]. It is now known that they are powerful activators of human genes involved in the synthesis of anti-oxidant enzymes, modulation of anti-inflammatory pathways, and activation of anti-aging genes as well as critical factors to maintaining a healthy gut microbiota and maintaining the efficacy of the mitochondria.

There is a great deal of epidemiological data to show that increased dietary intake of food components rich in polyphenols (vegetables, fruits, nuts, and whole grains) are associated with lower rates of chronic disease and mortality[2,3]. Furthermore, increased levels of polyphenols in the urine (indicative of their degree of bioavailability) are strongly associated with reduced mortality and frailty in elderly populations[4,5].

Potential mechanisms of polyphenols on human health

Although polyphenols can act in a non-specific manner as free radical scavengers, it is increasingly clear that the complexity of their benefits for human health may lie in three distinct areas. These are (a) their effect on gene expression in human cells, (b) their effect on the gut microbiota, and (c) their ability to maintain mitochondrial health.

Gene Expression

The most intriguing mechanism of polyphenol actions on human cells is their ability to activate key genes, in particular those involved in the production of anti-oxidant enzymes, reduction of inflammatory responses, and activation of genes associated with a reduced rate of aging.

Antioxidants Actions

Although polyphenols have classical non-specific anti-oxidant actions like vitamin E and vitamin C, they also have the ability to activate of anti-oxidative genes such as Nrf2[6-8]. Once these genes are activated, they generate increased expression of anti-oxidative enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase. Unlike typical dietary non-specific anti-oxidants such a vitamin E or vitamin C, these anti-oxidative enzymes are thousands of times more effective in removing excess free radicals. The reduction of the excess free radicals and their associated decrease of oxidative stress have been associated with decreased mortality[9].

Anti-inflammatory Actions

Certain polyphenols have been shown to inhibit the binding of the inflammatory gene transcription factor known as nuclear factor kappaB (NF-κB) to its binding sites in the nucleus (10). The anti-inflammatory actions of polyphenols are also associated with their stimulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) (11-13). PPARγ controls lipid uptake, fat cell synthesis and inflammation. Increased expression of this gene transcription factor also inhibits the activation of NF-κB, which is the master switch for turning on the innate inflammatory response[14-16].

Anti-Aging Actions

Finally polyphenols can activate the anti-aging gene (SIRT-1) that expresses increased levels of AMP kinase, which controls general metabolism and initiates autophagy[17-19].

The activation of all of these human genes depends on the levels of polyphenols in the blood. Since polyphenols generally have a poor bioavailability (5-10%), to activate these genes usually requires consuming large amounts of polyphenols in the diet[20].

Gut Health

The role of polyphenols in gut health is even more complex. One important purpose for polyphenols in the gut is their ability to be a primary defense against pathological microbial invaders as they do for plants. In particular, polyphenols appear to interfere with the quorum sensing actions of bacteria thus disrupting biofilm formation used by many pathogenic bacteria to circumvent host defense systems[21-23]. Polyphenols also enhance the production of those unique strains of bacteria (such as *Akkermansia muciniphila*) in the gut microbiota that appear to act as a master switch for controlling the gut microbiota. This is especially important for the improvement of the integrity of the mucus barrier and tight junctions of the mucosal cells to prevent entry of bacterial fragments such a lipopolysaccharide (LPS) into the blood[24-26]. As the levels of LPS increase in the blood, they interact with toll-like receptors (in particular TLR-4) to generate low-level chronic inflammation leading to metabolic endotoxemia with a corresponding increase in obesity and diabetes[27].

Whereas the poor availability of polyphenols is rate limiting on their ability to activate gene transcription factors in human cells, the same low absorption by the small intestine allows a targeted delivery to the colon and the microbiota in that region.

Within the colon, a great deal of metabolic modification of polyphenols takes place, although much of the details of that metabolism remain unknown. It is estimated that a high percentage of the metabolites in the blood come from the gut metabolism of polyphenols[28,29]. Since the lifetime of polyphenol metabolites in the blood is relatively short, a relatively constant dietary intake of polyphenols could be required to maintain optimal levels in the colon to ensure adequate levels of their metabolites in the blood.

Mitochondrial Health

Although mitochondria are found in every living cell and generate the vast majority of energy needed for cell viability, these organelles have far more in common with bacteria than with eukaryotic cells. Our best estimates are that certain types of bacteria became endosymbionts within other bacteria more than 2 billion years ago. Over the next 800 million years there was a gradual evolution that transferred most of the genes of the engulfed bacteria into the DNA of the host cell, while still retaining some of their genes internally. Once this was accomplished, the stage was set for multi-cellular life to develop as it required much larger amounts of chemical energy (such as ATP) to be produced than could be done by fermentation alone[30,31].

The volume of a human cell is typically 100,000 times greater than the volume of a single mitochondria even though the mitochondria produce 85-90% of the energy needs of the cell. Depending on the energy requirements of the particular cell, the number of mitochondria within a cell can range from a few (as in a white fat cell) up to 2,000 (as in liver and muscle cells).

Mitochondria are significant generators of free radicals in the process of converting glucose and fat into chemical energy (ATP). If the coupling of free radical generation to the production of ATP becomes uncoupled, then this can lead to excess generation of reactive oxygen species (ROS). Since the DNA inside each mitochondrion is directly exposed to any excess ROS generation, the mitochondrial DNA can become easily damaged and the efficiency of that particular mitochondrion becomes compromised. Damaged mitochondria have to be rapidly replaced before further oxidative damage spreads to the nuclear DNA of the cell as well as resulting in oxidative damage to lipid and proteins within the cell. This is why the lifetime of a typical mitochrondria is usually two weeks (32), whereas the lifetime of a typical human cell is 10 years[33-35]. As a result, there is a need for a constant synthesis of new mitochondria (i.e. biogenesis) coupled with the simultaneous removal of damaged mitochondria (i.e. mitophagy) in a highly coordinated action so as not to reduce the continuous production of ATP needed by the cell[36]. The key signaling factor that controls both functions (biogenesis and mitophagy) is AMP kinase. The activity levels of this key enzyme can be increased by polyphenols via the activation of the SIRT-1 gene[37,38].

Polyphenol Extracts

Regardless of the potential of polyphenols for gene activation, improved gut and mitochondrial health, their levels in foods are very low. As an example, the levels of polyphenols in vegetables are usually about 0.1% of their weight and only slightly higher (0.2% by weight) in fruits. Thus consistent consumption of adequate levels of fruits and vegetables may be required to supply adequate intakes of polyphenols for potential clinical benefits.

However, plants sources can be processed to yield polyphenol extracts that contain polyphenol concentration greater than 40% by weight (39). The extraction methodology for polyphenol extracts starts with dehydration of the food source to give a dry powder. This dehydration step usually doubles the polyphenol concentration. The dried powder can be further extracted by alcohol to increase the polyphenol content. This is because polyphenols have higher solubility in alcohol compared to other plant components. This explains why red wine can be considered to be the first polyphenol extract. However, the alcoholic extracts can be even further purified by chromatography to generate even more refined polyphenol extracts[40].

Human trials

Purified polyphenol extracts allow for human clinical studies to demonstrate their therapeutic efficacy. To date, three groups of polyphenols have been shown to have therapeutic benefits under clinically controlled experiments. The most validated are members of the flavonoid family of polyphenols. These polyphenols are characterized by two fused phenol rings, which may impart special spatial characteristics to enhance their biological actions[41]. These flavonoids include cocoa flavanols, anthocyanins, and finally a subclass of anthocyanins known as delphindins.

Cocoa flavanols in high concentration (a minimum of 450 mg per day) have demonstrated benefits in vascular flow and improving cognitive function as well as the size of the hippocampus[42,43]. Anthocyanin extracts from blueberries have demonstrated improvements in cognitive function and reduction in oxidized LDL cholesterol[44,45], and delphindins extracts from the maqui berry have benefits in reducing glycemia, oxidative stress as measured by isoprostanes, as well as reducing oxidized LDL cholesterol levels[46-49].

However, these clinical benefits may come from the direct entry of the polyphenols into the blood. In this respect, the delphinidins from the maqui berry are interesting as this class of polyphenols is known to be absorbed intact compared to other polyphenols[50]. Improved bioavailability is important as demonstrated in epidemiological studies in which the levels of the polyphenols in the urine are strongly with both reduced mortality and frailty[4,5].

What are adequate intake levels for polyphenol extracts?

The answer depends on what genes you are trying to activate. A general suggestion might be the following[51,52]:

Gene	Benefit	Polyphenols required
Nrf2	Reduce oxidative stress	500 mg per day
PPAR	Reduce inflammation and improve gut health	1000 mg per day
SIRT-1	Reduce the rate of aging and improve mitochondrial health	1500 mg per day

A standard serving of a fruit or a vegetable will contain about 100 mg of polyphenols. Therefore to reach a level of 1000 mg of polyphenols per day would require consuming approximately 10 servings of fruits and vegetables daily. This is also a formidable dietary task. Therefore to reach those levels will generally require the use of polyphenol extracts. However, once those therapeutic levels are reached, significant clinical benefits could be observed.

Summary

Polyphenols can potentially generate a remarkable range of beneficial effects in human cells, in the gut microbiota, and in controlling mitochondria quality and function. Because of the recently described metabolic actions, dietary polyphenols have a potentially unique role to play in the management of chronic diseases associated with increased inflammation and oxidative stress. The key to this potential goal is the consumption of adequate levels of polyphenols to activate these metabolic effects. The use of polyphenol extracts makes reaching that potential goal more likely.

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