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Green Tea Polyphenolic Compounds and Human Health

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Abstract: Polyphenols are a structurally diverse group of compounds that occur widely throughout the plant kingdom. Polyphenolic compounds are ubiquitous in all plant organs and are, therefore, an integral part of the human diet. Recent interest in food phenolics has increased greatly because of the antioxidant and free radical-scavenging abilities associated with some phenolics and their potential effects on human health.

Most of the polyphenols in green tea are commonly known as catechins. The regular consumption of green tea is related to benefits in some diseases as atherosclerosis and cancer. Although consumption of dietary polyphenols such as flavonoids has been suggested to have beneficial biological effects, there are considerable evidences to suggest that such compounds are not without risk of adverse effects.

Zusammenfassung: Zu den Polyphenolen gehören strukturell sehr unterschiedliche Substanzen, die im Pflanzenreich weit verbreitet sind. Polyphenolische Substanzen treten ubiquitär in allen Pflanzenteilen auf und sind damit auch ein integraler Bestandteil der menschlichen Ernährung. Kürzlich hat das Interesse an diesen phenolischen Substanzen in Lebensmitteln stark zugenommen, weil einige von ihnen die Befähigung zum Abfangen von schädigenden Stoffen und damit Auswirkung auf die menschliche Gesundheit haben sollen.

Die meisten Polyphenole im Grünen Tee sind als Catechine bekannt. Der regelmäßige Konsum von Grünem Tee wird positiv in Bezug auf die Abwehr einiger Krankheiten wie etwa Arteriosklerose und Krebs gewertet. Obwohl der Aufnahme von Polyphenolen mit der Nahrung, wie z. B. von Flavonoiden, gesundheitsfördernde Auswirkungen zugeschrieben wird, gibt es aber auch bedenkenswerte Hinweise dafür, dass mit diesen Substanzen das Risiko gegenteiliger Auswirkungen verbunden sein könnte.

1. Polyphenols in Foods

Polyphenols are a structurally diverse group of compounds that occur widely throughout the plant kingdom (Robbins et al., 2006). Polyphenolic compounds are ubiquitous in all plant organs and are, therefore, an integral part of the human diet. Until recently, most of the nutritional interest in these substances was in the deleterious effects caused by the ability of certain polyphenols to bind and precipitate macromolecules such as dietary protein, carbohydrate and digestive enzymes, thereby reducing food digestibility. Recent interest, however, in food phenolics has increased greatly because of the antioxidant and free radical-scavenging abilities associated with some phenolics and their potential effects on human health (Bravo, 1998). Several thousand molecules having a polyphenol structure (several hydroxyl groups on aromatic rings) have been identified in higher plants and several hundred are found in edible plants. These molecules are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens (Manach et al., 2004). Polyphenols are partially responsible for the sensory and nutritional qualities of plant foods. The astringency and bitterness of foods and beverages can be due to the content of polyphenolic compounds (Bravo, 1998; Cheynier, 2005). Fig. 1 shows a basic classification of polyphenols.

These compounds may be classified into different groups as a function of the number of phenol rings that they contain and of the structural elements that bind rings to one another. Distinctions are thus made between the phenolic acids, flavonoids, stilbenes and lignans (Fig. 2).

The flavonoids (Fig. 3), which share a common structure consisting of 2 aromatic rings (A and B) that are bound together by 3 carbon atoms that form an oxygenated heterocycle (ring C), may themselves be divided into 6 subclasses as a function of the type of heterocycle involved: flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (catechins and proanthocyanidins) as we can see in Fig. 1. In addition to this diversity, polyphenols may be associated with

Fig. 1 Classification scheme for polyphenols.

various carbohydrates and organic acids and with one another (Manach et al., 2004).

2. Antioxidant (and Beyond) Action of Polyphenols

Often, flavonoid antioxidant effects are conceived only in terms of a single biochemical action, direct reactions with radicals (Di Silvestro, 2001). The antioxidant capacity of these phenolic compounds is essentially due to the ease with which a hydrogen atom from an aromatic hydroxyl (OH) group can be donated to a free radical, and the ability of an aromatic compound to support an unpaired electron as a result of delocalization around the μ-electron system. The effects of substituent groups in various positions have been studied in depth, especially in the case of flavonoids. The most important structural determinants appear to be the 4'-OH group and 3-OH groups. The subsequent addition of hydroxyl groups to the carbon atoms ortho to the 4'-C position further increases antioxidant potential. Reaction rate constants in organic media for several flavonoids exceed that of vitamin E, our most important lipid-soluble antioxidant. This may be because they have (i) a more extended conjugated system to support an unpaired electron, (ii) two or more reactive OH groups, and (iii) less stearic hindrance at the site of abstraction (Duthie and Crozier, 2000). Recent studies confirm that many flavonoids and other phenolics are effective antioxidants in a wide range of chemical oxidation systems, being capable, for example, of scavenging peroxyl radicals, alkyl peroxyl radicals, superoxide, hydroxyl radicals and peroxynitrite in aqueous and organic environments (Bravo, 1998; Camargo et al., 2006).

Although direct radical scavenging is thinking like a single mechanism, this action could involve more than one type of reaction within an oxidant process (Di Silvestro, 2001). The table 1 lists possible antioxidant mechanisms of flavonoids.

The use of several flavonoids results in a reduction in ischemia-reperfusion injury by interfering with inducible nitric-oxide synthase activity. Nitric oxide is produced by several different types of cells, including endothelial cells and macrophages. The much higher concentrations of nitric oxide

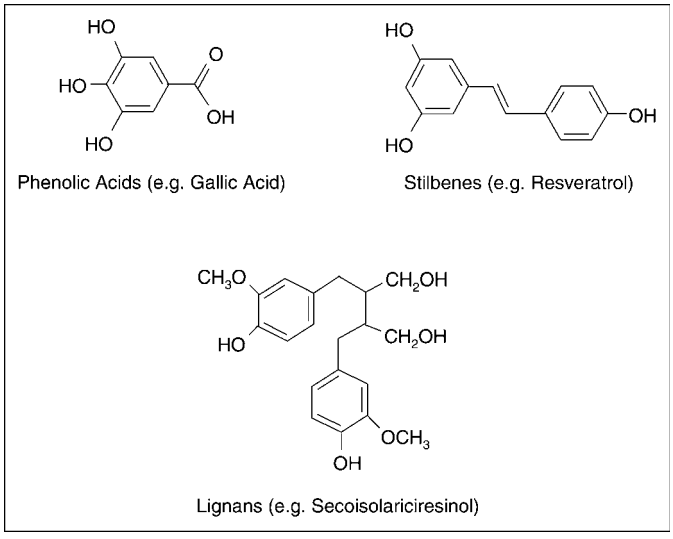

Fig. 2 Chemical structures of polyphenols.

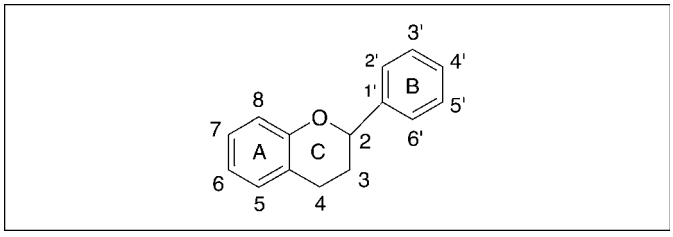

Fig. 3 Basic structure and numbering system of flavonoids.

Tab. 1 Possible antioxidant mechanisms of flavonoids (adapted from Di Silvestro, 2001).

1) Direct radical scavenging
2) Elimination of radical precursors (i.e., nitric oxide, hydrogen peroxide)
3) Metal chelation
4) Inhibition of xanthine oxidase
5) Elevation of endogenous antioxidants
6) Leukocyte immobilization
7) Inhibition of NF-kB activation
8) Down regulation of radical production

produced by inducible nitric-oxide synthase in macrophages can result in oxidative damage. Nitric oxide reacts with free radicals, thereby producing the highly damaging peroxynitrite. When flavonoids are used as antioxidants, free radicals are scavenged and therefore can no longer react with nitric oxide, resulting in less damage (Nijveldt et al., 2001). Moreover, prevention of the formation of free radicals includes down regulation of the production of superoxide radical and hydrogen peroxide, another precursor of free radicals (Di Silvestro, 2001).

Another way flavonoids may prevent radical formation is by chelation of transition metals. Some transition metals, such as iron, can catalytically form reactive free radicals. Many flavonoid structures have the chemical properties to chelate these metals in a state where radical generation is inhibited. In addition to this action, metals and flavonoids may also, in some circumstances, form complexes which actually eliminate radicals (Di Silvestro, 2001).

The xanthine oxidase pathway has been implicated as an important route in the oxidative injury to tissues, especially after ischemia-reperfusion. Both xanthine dehydrogenase and xanthine oxidase are involved in the metabolism of xanthine to uric acid. Xanthine dehydrogenase is the form of the enzyme present under physiologic conditions, but its configuration is changed to xanthine oxidase during ischemic conditions. Xanthine oxidase is a source of oxygen free radicals. Flavonoids can inhibit xanthine oxidase activity, thereby resulting in decreased oxidative injury (Nijveldt et al., 2001).

There is another possible indirect antioxidant action of flavonoids. Some of these compounds may elevate body concentrations of endogenous antioxidants which themselves eliminate free radicals or their precursors. An example would be superoxide dismutase, which eliminates superoxide radical inside cells (Di Silvestro, 2001).

The immobilization and firm adhesion of leukocytes to the endothelial wall is another major mechanism responsible for the formation of oxygen-derived free radicals, but also for the release of cytotoxic oxidants and inflammatory mediators and further activation of the complement system. Under normal conditions, leukocytes move freely along the endothelial wall. However, during ischemia and inflammation, various mainly endothelium-derived mediators and complement factors may cause adhesion of the leukocytes to the endothelial wall, thereby immobilizing them and stimulating degranulation of the neutrophil. As a result, oxidants and inflammatory mediators are released, resulting in injury to tissues. The decrease in the number of immobilized leukocytes by flavonoids may be related to the decrease in total serum complement and is a protective mechanism against inflammation-like conditions associated with, for example, reperfusion injury (Nijveldt et al., 2001).

Nuclear factor-κB is a transcriptional factor required for the gene expression on many inflammatory mediators. Nuclear factor-κB activation requires removal and degradation of its inhibitor κB, an event that occurs after phosphorylation of inhibitor κB by a complex of inhibitor κB kinases. These events allow nuclear factor- κB to translocate into the nucleus, where it binds to κB elements and initiates transcription. Inappropriate and prolonged activation of nuclear factor- κB has been linked to several disease associated with inflammatory events, including septic shock, acute respiratory distress syndrome, ischemia and reperfusion injury. Thus, the key role of nuclear factor- κB in regulating inflammation makes this factor a therapeutic target for reducing tissue and organ damage. Regulation and control of nuclear factor-κB can be achieved by gene modification strategies or by pharmacologic inhibition of the key components of the cascade that leads to nuclear factor- κB activation (Nijveldt et al., 2001). Green tea has shown remarkable anti-inflammatory and cancer chemopreventive effects in many animal tumor bioassays, cell culture system and epidemiologic studies. These biological effects of green

tea are mediated by tea catechins, which may inhibit NF-κB activation (Zingarelli et al., 2003).

Recently, flavonols and their metabolites were suggested to act by modulating cell signaling pathway *in vivo*, such as phosphoinositide 3-kinase, protein kinase B (AKT/PKB), tyrosine kinase, protein kinase C and mitogen-activated protein kinase (Williams et al., 2004). Protein kinase C is thought to trigger secretion of superoxide and hydrogen peroxide (Di Silvestro, 2001). These studies eclipse the conventional view of a simplistic antioxidant activity (hydrogen donator) of flavonoids (Williams et al., 2004).

3. Catechins of Green Tea

The tea plant *Camellia sinensis* is believed to have been originally discovered and grown in Southeast Asia. Tea consumption can be traced back to 2737 B.C., when, as believed by the Chinese, the emperor of China, Shen Nung, discovered and used tea for the first time (Ahmad and Muktar, 1999). Although consumption levels vary widely around the world, it is believed that tea consumption is second only to water, with a per capita human consumption of approximately 120 mL/day (Ahmad and Muktar, 1999). The chemical composition of green tea, with regard to its major components, is similar to that of the fresh leaves of the plant. It contains many of polyphenolic compounds, which account for up to 30% of the dry weight of green tea leaves. Most of the polyphenols in green tea are flavanols, commonly known as catechins. The primary catechins in green tea are (-)epicatechin (EC), (-)epicatechin-3-gallate (ECG), (-)epigallocatechin (EGC), and (-)epigallocatechin-3-gallate (EGCG). In addition, caffeine, theobromine, theophylline, and phenolic acids, such as gallic acid, are also present as minor constituents of green tea (Ahmad and Muktar, 1999). Depending on soil quality and micronutrient content, tea also provides small amounts of fluoride and other micronutrients (Weisburger, 1999; Cai and Chow, 2004).

Black tea is made by promoting enzymatic oxidation of fresh leaves. Most flavanols are converted to the oxidized form known as theaflavins and thearubigins. The total flavanol level is reduced from 35 to 50% in green tea to 10% in black tea. Theaflavins and thearubigins are present in black tea at a level of 3 to 6% and 12 to 18%, respectively. All other components are virtually unchanged. Oolong tea is a half-fermented product. It contains monomeric catechins, theaflavins and thearubigins with a catechin level of 8 to 20% of the total dry matter (Cai and Chow, 2004).

4. Green Tea and Cardiovascular Disease

Oxidative damage to lipoproteins, particularly low-density lipoprotein (LDL), can produce modified particles containing both lipid products and damaged apoprotein. These oxidized particles (LDLox) have enhanced atherogenic effects. The LDL oxidation hypothesis in cardiovascular disease suggests that LDLox contributes to all stages of the atherosclerotic process, including activation of inflammatory events, endothelial damage, recruitment of macrophages and unregulated uptake of LDLox by these cells to form foam cells, the hallmark of early atherosclerotic lesions. While a critical role for LDLox in atherogenesis is now well supported, the actual pathways that promote LDLox *in vivo* have been difficult to identify. Oxidation is thought to occur in the subendothelial space of the arterial wall and recent analysis of stable compounds that result from specific pathways suggests that both reactive species of oxygen (ROS) and reactive species of nitrogen (RNS) as well as enzymes, such as myeloperoxidase and lipoxygenase, may be involved (Morton et al., 2000). It has been hypothesized that catechins might be localized near the membrane surface scavenging aqueous phase radicals and preventing the consumption of α-tocopherol, whereas the latter mainly act as a scavenger of lipid peroxyl radicals within the LDL (Salah et al., 1995). Moreover, the effect of food polyphenols on lipid metabolism has been studied. Both soluble polyphenols and condensed tannins have been shown to increase fecal fat excretion. In addition, hypocholesterolemic effects have been reported in animals fed diets containing grape tannins, tannic acid and tea catechins with increased plasma levels of high density lipoprotein (HDL) cholesterol and reduced concentrations of LDL cholesterol. This hypocholesterolemic action of dietary polyphenols is mediated by an enhanced reverse-cholesterol transport and by reduced intestinal cholesterol absorption and increased bile acid excretion. The exact mechanism of action, however, is not known (Bravo, 1998). Many studies directly measuring free radicals in experimental models of ischemia have found that the magnitude of the free radical generation after reperfusion is proportional to the magnitude of the flow deficit during the antecedent coronary occlusion. These studies support the hypothesis that administration of antioxidants prior the onset of ischemia may reduce tissue damage and suggest the importance of future researches in this direction.

In this light, green tea consumption could be of particular importance (Bordoni et al., 2002). EGCG, the major catechin component in green tea, selectively prevents cytokine-induced VCAM-1 expression and reduces monocyte adhesion to endothelial cells independently of NF-κ-B activation. Since VCAM-1 is one of the key molecules involved in the early atherogenic process, this emphasize a novel mechanism by which tea catechins may exert antiatherogenic effects (Ludwig et al., 2004). Independent of the mechanism, cardiovascular health appears to be better among tea drinkers than non-tea drinkers. More specifically, the incidence of ischemic heart disease (including myocardial infarct and stroke) is lower in tea drinkers compared with non-tea drinkers (Trevisanato and Kim, 2000). In a Japanese study, although green tea consumption was unrelated to serum HDL-cholesterol and triglycerides, the consumption of this beverage was associated with lower serum concentration of total cholesterol in healthy workers age 40–69 years (Tokunaga et al., 2002). Still in Japan, the Ohsaki Study investigated the associations between green tea consumption and all-cause and cause-specific mortality. Green tea consumption was associated with reduced mortality due to all causes and due to cardiovascular disease (Kuriyama et al., 2006). The Rotterdam Study was a prospective study in

the general Dutch population to assess the association of tea and flavonoid intake with incident myocardial infarction. The findings in the Rotterdam Study suggested a protective effect of tea and flavonoid intakes against ischemic heart disease (Geleijnse et al., 2002).

5. Green Tea and Cancer

Extensive epidemiological studies have established unequivocally that consumption of diets rich in fruits and vegetables reduces the incidence of cancer at specific sites, as well as the overall cancer incidence, so that the public are continuously encouraged to shift their dietary patterns to such diets (Ioannides and Yoxall, 2003). Different types of polyphenols (phenolic acids, hydrolysable tannins and flavonoids) have been shown to have anticarcinogenic effects. Polyphenols might interfere in several of the steps that lead to the development of malignant tumors, thereby protecting DNA from oxidative damage, inactivating carcinogens, inhibiting the expression of mutant genes and the activity of enzymes involved in the activation of procarcinogens and activating enzymatic systems involved in the detoxification of xenobiotics (Bravo, 1998). The anticarcinogenic and antimutagenic properties of green tea were first elucidated several years ago. Since then, several laboratory and epidemiologic studies have been conducted (Ahmad and Mukhtar, 1999). Two mechanisms are responsible for the *in vitro* antimutagenic activity expressed by tea. The first and most important mechanism involves inhibition of the bioactivation of chemical carcinogens to produce the reactive genotoxic intermediates. Components of tea impair the activity of cytochromes P450, the enzyme system that is responsible for the bioactivation of most chemical carcinogens, and in this way suppress the formation of the DNA-binding metabolites. The second mechanism entails direct interaction of component(s) of tea with the reactive metabolites of carcinogens, thus preventing them from binding to the DNA (Ioannides and Yoxall, 2003). Other mechanisms that should be considered are inhibition of biochemical markers of tumor initiation and promotion, effects on detoxification enzymes and antioxidant and free-radical scavenging activity (Ahmad and Mukhtar, 1999).

Although experimental studies have shown consistently that tea preparations and tea polyphenols may inhibit the induction of a variety of cancers, including lung cancer, epidemiologic studies of tea consumption and cancer are limited and the results are inconclusive. Different research groups have reviewed the available data and they have all concluded that more epidemiologic data are needed to determine whether drinking green and black teas reduces the risk of cancer (Zhong et al., 2001).

6. Other Pathological Conditions

The use of polyphenols, in particular of green tea, is related with some benefit to other pathological conditions. A great study in Finland demonstrates that the risk of some chronic diseases may be lower at higher dietary flavonoid intakes. A trend toward a reduction in risk of type 2 diabetes was associated with higher quercetin and myricetin intakes (Knekt et al., 2002). Another study in Taiwan supports the concept that oolong tea is effective in lowering the plasma glucose levels of subjects who have type 2 diabetes and who take oral antihyperglycemic agents. Furthemore oolong tea in conjunction with antihyperglycemic agents was more effective in lowering plasma glucose than the drugs alone (Hsoda et al., 2003). A Japanese cohort study showed an inverse association between green tea, coffee and caffeine consumption and the risk for diabetes in women and in overweight men. But the authors alerted that clinical trials are necessary to confirm the protective effect of green tea and coffee for type 2 diabetes. Green or oolong tea are majors sources of caffeine in Asian countries. The mechanisms responsible for the inverse association between caffeine intake and diabetes risk include increased basal energy expenditure, stimulation of fat oxidation and mobilization of glycogen in muscles and stimulation of free fatty acid release (increased lipolysis) from peripheral tissues (Iso et al., 2006). Besides these potential effects of caffeine, antioxidant substances such as epigallocatechin gallate from green tea may have beneficial effects on the risk for diabetes through their action on insulin resistance and glucose metabolism (Waltner-Law et al., 2002; Song et al., 2003).

Consumption of tea polyphenols may have beneficial effects on brain function. Brain tissue contains high levels of oxidation substrates (such as unsaturated fatty acids) and catalytically active metals (such as iron and copper) and is sensitive to free radical assault. Several studies have demonstrated that green tea polyphenols may be neuron protective by reducing the tissue injury and functional impairment associated with reactive oxygen species. Specifically in relation to Parkinson's disease, green tea polyphenols may exert neuroprotection through antioxidant effects. The inhibition of dopamine transporter (DAT) which is a functional protein involved in the re-uptake of dopamine released into synaptic clefts and is thought to be a link between environmental neurotoxins and this disease. The increase of the bioavailability of levodopa in the treatment and finally, the antiapoptotic properties of green tea polyphenols may offer therapeutic benefits in Parkinson's disease (Pan et al., 2003).

Streptococcus mutans has been shown to induce dental caries in experimental animals as well as humans. In the oral cavity, the bacterium synthesizes adhesive and water-insoluble glucan from sucrose by the action of glucosyltransferases and firmly adheres to tooth surfaces, wich contributes to the induction of dental caries. Oolong tea extract was found to contain antibacterial substances against *Streptococcus mutans*, which were shown to be composed of monomeric polyphenols. This bactericidal activity was demonstrated to originate from the synergistic effect of monomeric polyphenols (Sasaki et al., 2003).

Finally, in an experimental study with rats it was found that the inhibitory effect of green tea on calcium oxalate urolithiasis is most likely due to antioxidant effects (Itoh et al., 2005).

7. The Other Side of the Coin

Dietary polyphenols have been widely touted as antioxidants and numerous studies have attributed the potential health beneficial effects of these compounds to their antioxidant activities. Whereas the antioxidant activities of these compounds have been demonstrated *in vitro*, it has been much harder to demonstrate a significant antioxidant activity *in vivo*. By contrast, there is an increasing body of evidence to suggest the pro-oxidative effects of polyphenols (Lambert et al., 2007). These prooxidative activities may have implications regarding potential toxicity. For example, the treatment of rat hepatocytes with 200μM EGCG reduced cell viability. Cell death was associated with increased production of reactive oxygen species and depletion of reduced glutathione (GSH) (Galati et al., 2006). Besides, intraperitoneal administration of EGCG resulted in the formation of two cisteine conjugates (EGCG-2'-cysteine and EGCG-2"-cysteine). These compounds were only formed at toxic doses of EGCG (200 and 400 mg/kg ip) (Lambert et al., 2007). Laboratory studies in rodents and dogs have supported the potential toxic effects of high doses of green tea-derived preparations (Isbrucker et al., 2005; Galati et al., 2006). One large issue in this whole area is whether these prooxidant actions can occur *in vivo*, and if so, under what circumstances. So far, the evidence for prooxidant actions of flavonoids has come primarily for studies done *in vitro*. However, if flavonoids continue to gain attention for possible health-promoting effects, the issue of prooxidant actions must also be addressed (Di Silvestro, 2001).

The metabolism of several common polyphenols is now reasonably well understood. Polyphenols are extensively altered during first-pass metabolism so that, typically, the molecular forms reaching the peripheral circulation and tissues are different from those present in foods. In general, the resulting metabolites are conjugates (e.g. sulfates and glucuronates) of the parent aglycone or conjugates of methylated parent aglycones. Catabolism of polyphenols in humans usually occurs only as a result of microbial activity in the (large) intestine (Kroon et al., 2004). Identification and measurement of the physiological polyphenol conjugates are key prerequisites to an understanding of the role of dietary polyphenols in human health. Some authors strongly recommend that all experiments using *in vitro* models to study biological responses to dietary polyphenols apply only physiologically relevant flavonoids and their conjugates at appropriate concentrations (Kroon et al., 2004).

8. Conclusion

In agreement with several studies *in vitro* and *in vivo* it is reasonable to imagine that polyphenols may have important applications in the prevention and treatment of some diseases. The catechins of green tea are very promising in function of their antioxidant (and others) biological activities. To fully understand the actual significance of food phenolics in the human health, it is necessary to investigate their mechanisms of action, bioavailability and to develop analytical methods that accurately characterize and quantify these substances in foods, culture cells, urine and blood. Although consumption of dietary polyphenols such as flavonoids has been suggested to have beneficial biological effects against some diseases, there are considerable evidences to suggest that such compounds are not without risk of adverse effects.

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