1 Efficacy of Tea in Human Health

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Abstract
Recent scientific findings on the effects of tea (*Camellia sinensis*) on human health are reviewed. Some mechanistic explanations are discussed in relation to the special nature of (-)-epigallocatechin-3-gallate which works not only as an antioxidant but also as pro-oxidant. Though there are still some discrepancies between the results in animal models and those of epidemiological studies, the reasons will be uncovered in the near future.

Keywords: antioxidant, chronic disease prevention, health effects, pro-oxidant, tea catechins

1.1 How the Physiological Effects Caused by Tea Drinking Attracted Humans

There are many legends which told us to explain why the people in ancient China began to drink tea. One of the stories told is about Wan Tu, the ancient Chinese emperor. He was banished to a remote southern part of China (Yunnan province) due to his cruel and tyrannizing governance. One day, he was sitting in the shade of a large bush in the area where *Camellia sinensis* grew and drank hot water. There, he found that some leaves were floating in the hot water. After he drank the brewed tea with the leaves, he felt excited and freed from fatigue (Wild, 1994).

It is now known that the leaves of tea (*C. sinensis*) contain caffeine (2–4% in dry leaves) and theobromine (~0.1%) both of which are soluble in hot water and show special physiological functions, such as stimulation of the central nervous system. It is also well known that the tea leaves contain a large amount of catechins (8–20% of the dry weight) of which the major one is (-)-epigallocatechin-3-gallate (EGCG) (Fig.1.1).

Tea catechins are oxidized to various dimerization products, theaflavins, theasinensins, and proantocyanidins and further to polymerization products, thearubigins, in the process of tea preparation (Fig. 1.1). The taste of tea is very unique: bitter, and astringent because of the presence of the above substances. It may be worth knowing that their contents are quite different depending on the species of *Camellia* leaves. The leaves of *C. sinensis*, *Camellia taliensis*, and *Camellia irrawadiensis* are all known to contain caffeine, theobromine, and catechins, but other

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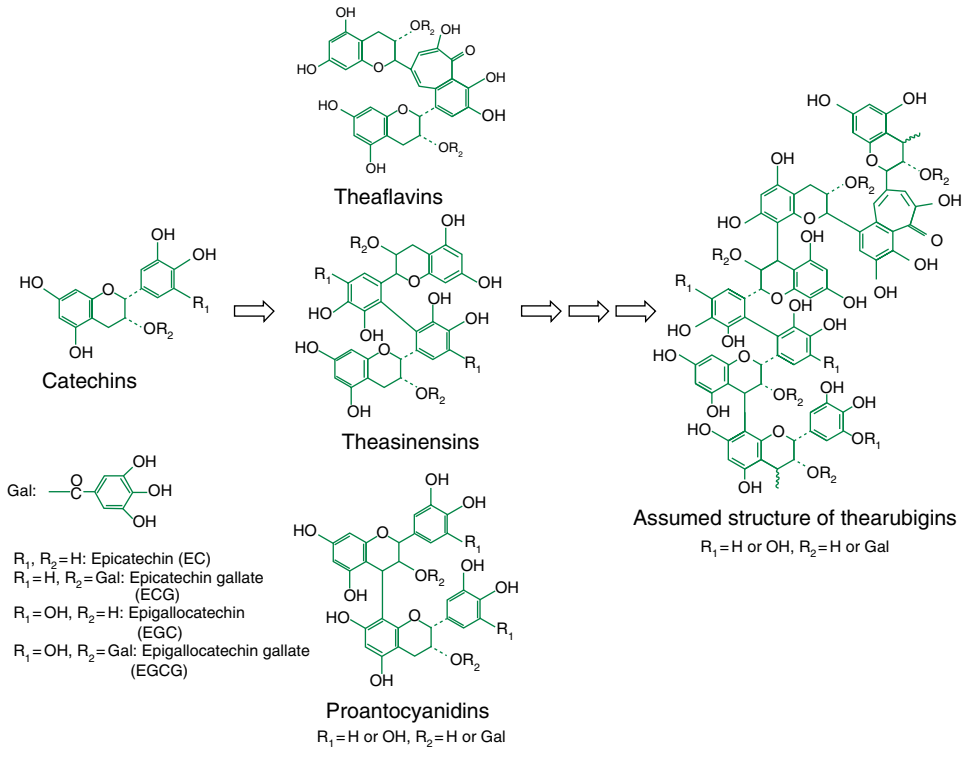

Fig. 1.1. Chemical structures of catechin and its related compounds. AIDS, acquired immune deficiency syndrome; RNS, reactive nitrogen species; ROS, reactive oxygen species; UV, ultraviolet.

species such as *Camellia furfuraceae* and *Camellia sasanqua* have no such components (Nagata and Sakai, 1984, 1985). Tea leaves are also known to contain the special amino acid, theanine (0.5–3%) which is rarely found in the plant kingdom.

1.2 Strong Antioxidant Properties of Tea and its Relation to Disease Prevention

Since tea drinking has a long history of more than 3000 years, there have been many scientific research studies on the nature of the components. These include isolation of the responsible substances for their characteristic taste, color, aroma, and physiological functions. However, it was not until the late 20th century that the research on tea as a "functional food (beverage)" was carried out. It was at this time that it was found that oxygen radicals, such as the superoxide anion radical ($\cdot O_2^-$) and the hydroxyl radical ($\cdot$OH) formed from "various stimulants", could cause degenerative disease and even aging. The term "oxidant stress" has become popular, and it was believed to be a main cause in developing diseases such as cancer, atherosclerosis, stroke, coronary heart disease, diabetes, and so on. The negative correlation between the mortality of such chronic diseases and the consumption of common vegetables and fruits containing various flavonoids as antioxidants seemed to accelerate this area of research (Hertog, 1996).

Cao *et al.* (1997) reported that tea has a very strong antioxidant activity compared with those of common vegetables in their ORAC (oxygen radical absorbing capacity) assay. We also recognized that the tea extracts as well as its main constituent, EGCG and its metabolites, exerted strong antioxidant

activities in rats (Tomita *et al.*, 1998). The development of evaluating methods for detection of antioxidant activities using TBARS (thiobarbituric acid reacting substances), 15-isoprostane F2t and 8-hydroxy-2′-deoxyguanosine as biomarkers contributed greatly to this area of research.

In another area of study at that time, a convenient method using microorganisms such as *Salmonella typhimurium* TA and *Escherichia coli* WP2 to detect mutagenic and antimutagenic substances was employed, and pioneering works on the antimutagenic properties of tea extracts were reported in 1984–1985 (Kuroda and Hara, 1999). Their anticarcinogenic effects in various assay systems at the stage of anti-initiation and anti-promotion were also demonstrated and reported (Nakamura *et al.*, 1997). General mechanisms of antimutagenesis and anticarcinogenesis were discussed in detail in the First International Conference which was held at the University of Kansas, USA in October 1985. The presentation on the effects of tea (extracts) seemed to attract successive research in different and diverse fields. Tea research done in the last 30 years has revealed that green as well as black tea will be the most common and acceptable beverage to avoid or decrease the risk of various diseases (Fig. 1.2).

However, now, we have to respond to the question: Why are the antioxidant effects of tea catechins and their related compounds so powerful despite their limited absorption into the body? Their absorption is less than 2–3% of the intake, and the maximum concentration in blood is only 0.03–0.38 μmole/l for EGCG ($T_{1/2}$ = 2.5–5.1 h) and it is far too low to expect direct antioxidant activity.

1.3 How Do Catechins Exert their Various Effects on Lifestyle-related Diseases?

In order to discuss the mechanistic explanation of tea catechins as the bio-antioxidant in connection to disease prevention, recent findings by several researchers on the effects of tea catechins for cell signaling or gene expression must be considered.

It is known that tea catechins as well as other flavonoids work as pro-oxidants (not only as an antioxidants) under some

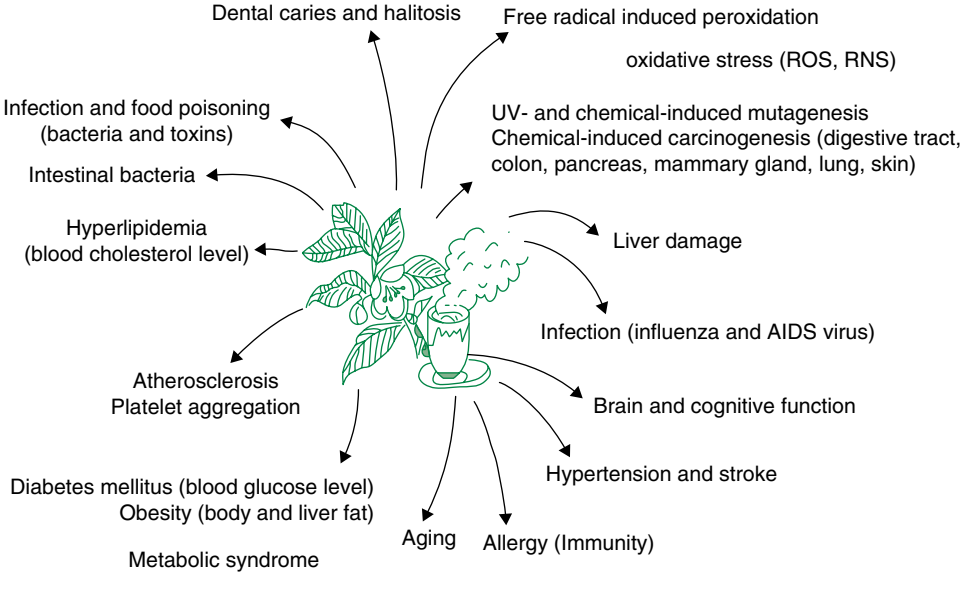

Fig. 1.2. Possible effects of tea on health. AIDS, acquired immune deficiency syndrome; RNS, reactive nitrogen species; ROS, reactive oxygen species; UV, ultraviolet.

experimental conditions and produce hydrogen peroxide (H_2O_2) *in vitro* and *in vivo* (Cao *et al.*, 1997; Miura *et al.*, 1998; Lambert and Elias, 2010). H_2O_2 is now known to be an important second messenger, transducing the oxidative signal into biological responses through post-translational protein modification (Forman *et al.*, 2004). In the case of excess H_2O_2 production, however, it might deteriorate vascular functions, for example promoting vascular diseases through multiple pathways (Shimokawa and Satoh, 2015). Adverse effects may occur by intake of a high amount of green tea extracts (GTE) containing EGCG, possibly due to the suppression of the activities of antioxidant enzymes such as catalase and peroxidase *in vivo* (Fig. 1.3).

The problems on EGCG-triggered hepatotoxicity and the safety of green tea drinking or intake as a dietary supplement have been extensively discussed (Sarma *et al.*, 2008; Navarro *et al.*, 2013, 2017; Mazzanti *et al.*, 2015; Teschke and Andrade, 2016). It might be related to the above H_2O_2 production, since the amounts of daily and long-time intake were quite excessive in these studies. For example, the intake of GTE from commercial tablets associated with hepatotoxicity is over 540 mg/day (Bonkovsky, 2006). Although some case reports suggest that liver failure may come from the daily intake of 400 mg EGCG (Patel *et al.*, 2013), the failure might be due not only to the amount of EGCG consumed, but also to the amount of the substances that coexisted in its dietary supplements. A recent report by Isomura *et al.* (2016), based on their work of randomized controlled trials in humans (odds ratio as the result of four principal reports of 800–1600 mg of EGCG intake was 2.1), suggests that liver-related adverse effects upon intake of GTE or EGCG would be not so serious as long as they are not consumed excessively. Anyway, we should be careful not to have excessive intake of GTE or EGCG, even if they are believed to be an excellent natural medicine. It has been said that "the last drop makes the cup run over". The potential hepatotoxicity of GTE or EGCG is also discussed in Chapter 20.

In contrast to the above discussion on the induction of hepatic failure in humans, beneficial effects of EGCG or GTE for not only viral hepatitis, but also non-alcoholic fatty liver disease of humans, have been suggested (Masterjohn and Bruno, 2012). These effects may be easily accepted, since EGCG has been known to have diverse effects such as lipid lowering (suppression of lipid synthesis, enhancement of insulin sensibility, and consumption of energy), suppression of lipid and glucose intake through the intestine, and anti-inflammatory activities, and hence it

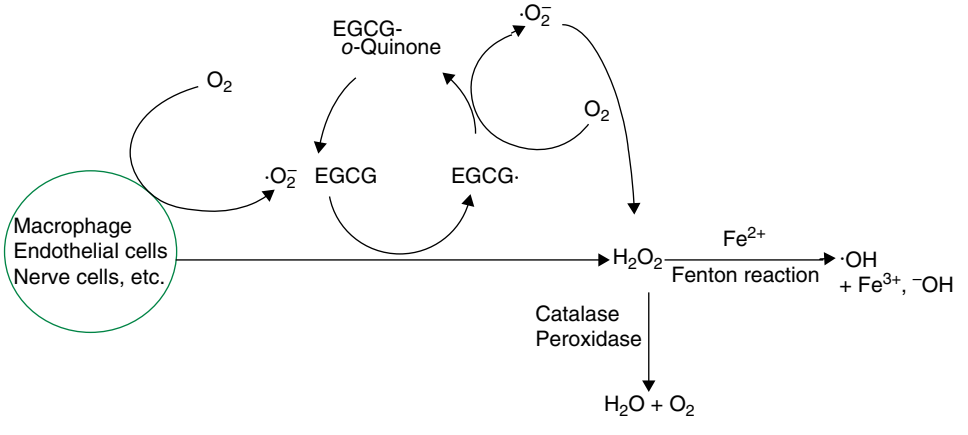

Fig. 1.3. Dual functions of (-)-epigallocatechin-3-gallate (EGCG). EGCG produces hydrogen peroxide (H_2O_2) under conditions of low activities of catalase/peroxidase. Hence, it acts as an antioxidant and pro-oxidant.

would contribute to body weight reduction and alleviation of a metabolic syndrome. The possible mechanistic explanation of these effects through AMP-activated protein kinase has been proposed recently (Yang and Hong, 2013; Yang *et al.*, 2016) (see also Chapters 7 and 8).

In recent years, on the other hand, the presence of many special binding molecules for EGCG have been reported, such as the 67 kDa laminin receptor (Tachibana *et al.*, 2004) (see also Chapter 10), vimentin (Ermakova *et al.*, 2005), insulin-like growth factor 1 receptor (Li *et al.*, 2007), tyrosine protein kinase Fyn (He *et al.*, 2008), and protein phosphatase 2A (Qin *et al.*, 2008) as well. It is expected that they may explain the role of catechins as powerful antioxidants even at low levels *in vivo*. It must be noted that catechins also have a role in activating the nuclear factor erythroid 2 related factor 2 and antioxidant response element (Shen *et al.*, 2005).

1.4 "Onko-Chishin"–He that would know what shall be, must consider what has been

Historically, tea (drinking) was introduced into Japan by several famous Buddhist priests who studied the doctrines of Zen Buddhism in China. Eisai was one of them. He visited and stayed in China twice (1167 and 1187) and learned about Zen in depth. Along with learning the religious discipline of Zen Buddhism, he devoted himself to tea, which kept him out of fatigue during his spiritual exercise and made him convinced that it was good for maintaining physical as well as spiritual health. At the age of 71 (1211), he wrote *Kissa Youjouki* (the way to prevent diseases by drinking tea). By quoting Chinese literature, he described his belief about the effectiveness of tea, for human health. There is an especially important statement in the latter part of the above book telling us that "The drug is for only one individual disease, while the tea prevents all kinds of diseases" ("Panacea").

The importance of tea for human health, not only for physical health but also for mental health, has been scientifically studied for the past 30 years. The significance of the presence of theanine in tea (about 1% in dry tea leaves) has been recognized and has drawn much attention in recent years. The main reason is that it might be a principal factor along with catechins to suppress cognitive dysfunction in the elderly. The details of the functions of theanine have been described by several authors including Yokogoshi *et al.* (1998) and these are also discussed in the current volume (see Chapters 22 and 24). There is a systematic review and meta-analysis on the effects of theanine, EGCG, and caffeine on cognitive function and mood (Camfield *et al.*, 2014). For the reference of readers, the numbers of research papers published in English on tea catechins up to the year 2016 are shown in Fig. 1.4. Though the numbers of scientific reports on theanine are not large, they are steadily increasing in recent years.

Finally, our present concern is that there still seems to exist some discrepancy between the fundamental research results using cells and animals and those of epidemiological studies in several areas of investigation. This might be one of the reasons why Dwyer and Peterson (2013) stated that: "Epidemiologic investigations should be of sufficient size and duration to detect small effects, involve populations most likely to benefit, use more complete tea exposure assessment, and include both intermediary markers of risk as well as morbidity and mortality outcomes." The answer to this issue must wait for several years until experimental and epidemiological sciences are more advanced. The interested reader is referred to several comprehensive reports (Hara, 2001; Suzuki *et al.*, 2012; Clifford *et al.*, 2013; Hursel *et al.*, 2013; Yuan, 2013; Kim *et al.*, 2014; Blumberg *et al.*, 2015; Chowdhury *et al.*, 2016; Momose *et al.*, 2016; Yang *et al.*, 2016) and the findings in other references listed below for a better appreciation of tea for human health.

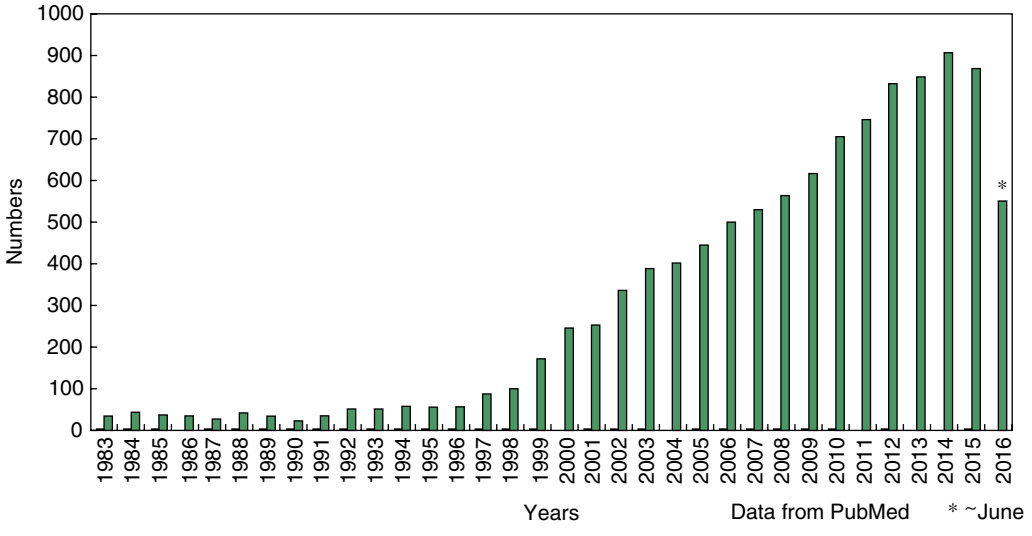

Fig. 1.4. Change in the number of research papers published in English on tea catechins over the period 1983 to September 2016.

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