Topical Review

Tea as preventive/protective against human diseases

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Introduction

Tea polyphenols constitute the majority of soluble solids in tea. In green tea, tea catechins which represent most of polyphenolic constituents remain in the dried leaves as they were in fresh tea shoots. Catechin fractions of various catechin content were extracted from green tea and four different individual catechins were purified. Over the last 20 years we have been investigating the various physiological actions of these catechins. Tea catechins have very potent antioxidative (radical scavenging) activity and the intake of them appears to suppress or retard the process of life-style related, life threatening diseases such as cancer, hyperlipidemia, hypertension, hyperglycemia. Tea catechins also have rather potent and unique anti-microbial potency that will inhibit the proliferation of infectious diseases, many of which plague our daily life. In the black tea manufacture, about three quarter of catechins in the fresh leaves are oxidized in the manufacturing process to form red-colored oligo-catechins that represent the red color of the black tea. Several oligo-catechins such as theaflavins are known to posses as potent physiological actions as catechins. Thus, the importance of tea drinking and the prophbylactic functions of tea catechins should be realized and valued highly not only in advanced countries where life style related, age related diseases are increasing but also in developing countires where newly emerging infectious diseases are threatening the health of people.

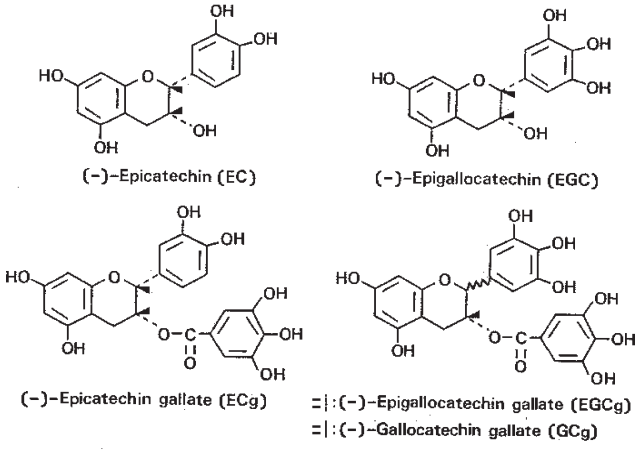

Fig. 1 Structural formulas of tea catechins

Variety of Catechins

There are four varieties of catechins in green tea, of which (-) epigallocatechin gallate (EGCg) is dominant and constitutes more than 50% of total catechins. The structural formulae of catechins are shown in Fig. 1. A simplified extraction method of tea catechins (Polyphenons™) is shown in Fig. 2, and an example of the breakdown of the individual catechin content is shown in Table 1. Total catechin content of "Polypehnons™" very from

Table 1 Composition of catechins in Polyphenons

Tea catechins	Polyphenon G	Polyphenon 30	Polyphenon 60	Polyphenon 100
(+) – Gallocatechin (+GC)	-	-	-	1.1
(–) – Epigallocatechin (EGC)	8.9	13.0	21.0	17.6
(–) – Epicatechin (EC)	4.9	3.8	7.3	5.8
(–) – Epigallocatechin gallate (EGCg)	17.3	15.0	29.2	53.9
(–) – Epicatechin gallate (EGCg)	4.4	3.5	7.9	12.5
Total	/35.3	/35.3	/65.4	/91.2

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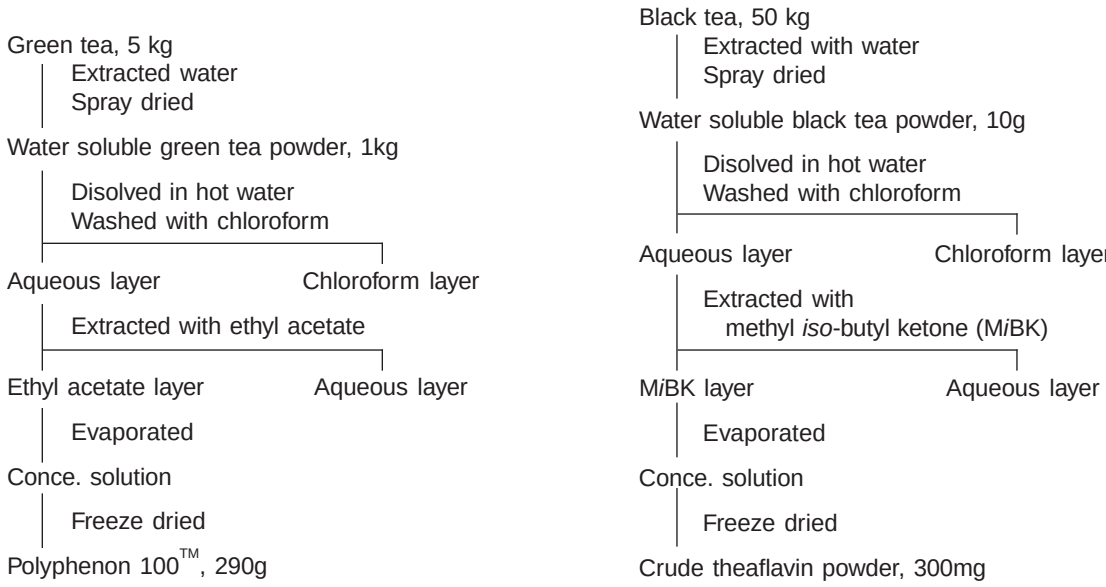

Fig. 2 Preparation of Polyphenon 100™ and crude theaflavins

30% to 90% according to the process. A simplified extraction method of theaflavins from black tea is also shown in Fig. 2.

Antioxidative Action

Lipid peroxidation, induced by boiling lard at 97.8°C with bubbling air, was suppressed by tea catechins as shown in Fig. 3 [1]. As shown in the figure, 10ppm of "Polyphenon 100" (90% catechin content) was as effective as 200ppm of α-tocopherol, ie. 20 times more potent than α-tocopherol. In the same way, "Polyphenon 100" was 5 times as effective as BHA. Notable radical scavenging potency of catechins was also confirmed by the reaction with DPPH radical [2].

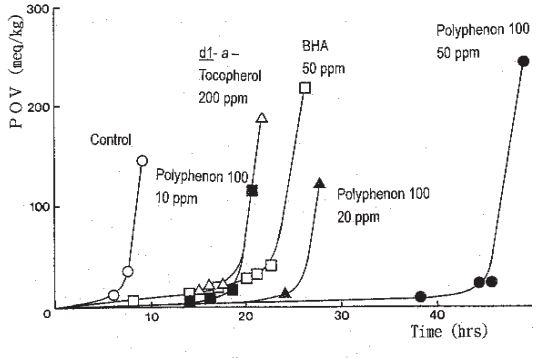

Fig. 3 Antioxidative activity of Polyphenon 100™ on the lard (AOM at 97.8℃)

Anti-tumor Action

Mice (ddY), fed diets containing 0.5% or 1.0% of catechin powder ("Polyphenon 100") for 9 months, were inoculated subcutaneously with sarcoma 180 cells. After 19 days, tumors were resected. As shown in Fig. 4, the growth of tumors was suppressed in catechin-fed groups in a dose-dependent fashion as compared with that of the control group [3].

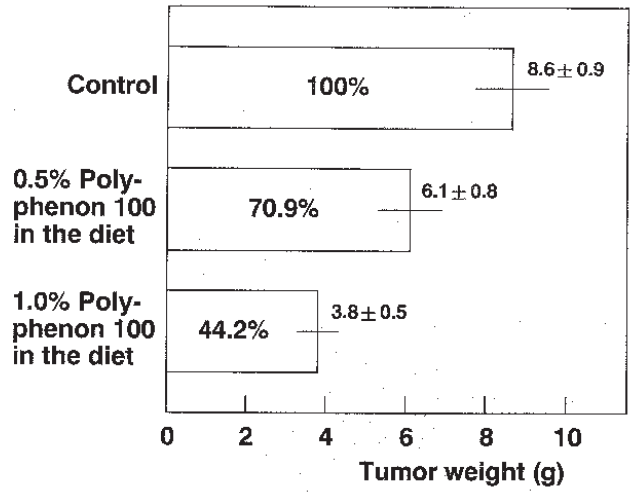

Fig. 4 Effect of Polyphenon 100™ on Sarcoma 180 bearing ddY mice

Anti-hyperlipidemic Action

Rats were fed a high fat, high cholesterol (15% lard, 15% sucrose, 1% cholesterol) diet to which a small amount of cholic acid (0.2%) was added to facilitate lipid absorption. After 4 weeks, all rats were sacrificed and their cholesterol levels were examined. The results in Fig. 5 show that the total cholesterol concentration of the test group rose to more than twice the level of that of the control group. Particularly, the LDL-cholesterol increased as much as 15 times and the HDL-cholesterol decreasd to less than half of the control values. But the addition of EGCg (0.5% or 1.0%) to the above test diet moderated the increase of LDL-cholesterol and the decrease of HDL-cholesterol dose-dependently [4].

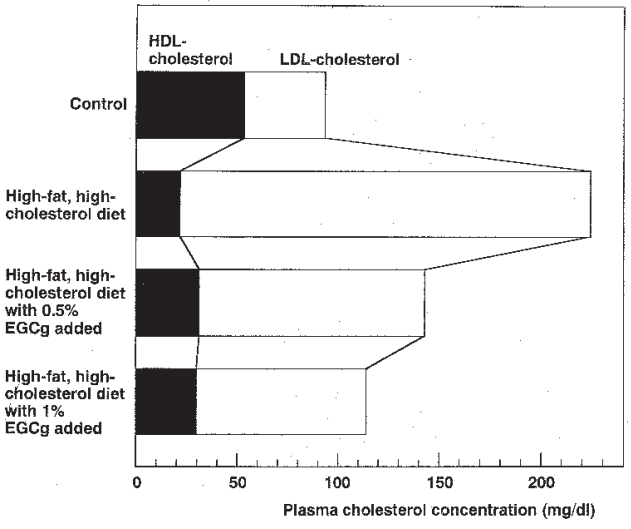

Fig. 5 Hypocholesterolemic effect of EGCg

Anti-hypertensive Action

Spontaneously hypertensive rats (SHR) were divided into two groups. The control group received a normal diet, while the test group was given 0.5% of "Polyphenon 100" in the diet from one week after weaning. As shown in Fig. 6, although the blood pressure in the control group exceeded 200mmHg at 10 weeks of age, significant suppression was noted in catechin fed group. When the diet of both groups was switched at 16 weeks of age, the blood pressures, in time, also changed accordingly [5].

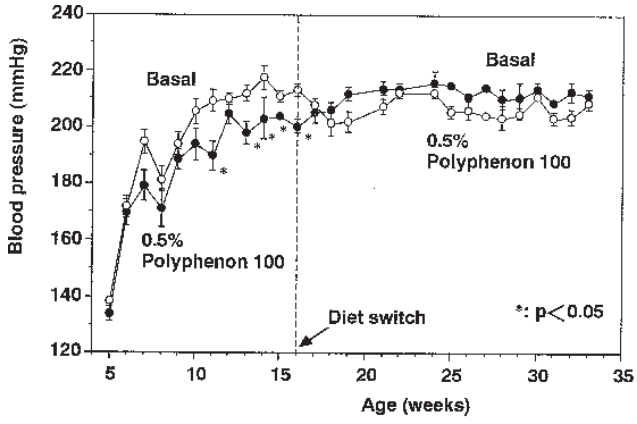

Fig. 6 Effect of Polyphenon 100™ on blood pressure of SHR

The effect of catechins on hypertension was also proven by the experiments with the stroke-prone SHR (Fig.7) the outbreak of brain strokes and the resultant deaths were prolonged by feeding 0.5% of Polyphenon100 in the diet.

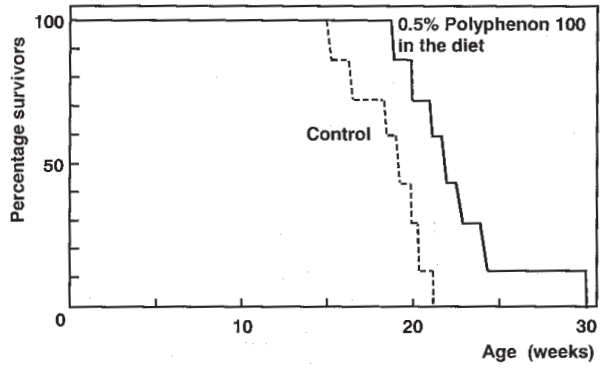

Fig. 7 Effect of Polyphenon 100™ on the life span of SHRSP.

Anti-hyperglycemic Action

Wistar rats were divided into two groups. They were starved overnight. 80mg of "Polyphenon 100" in 1 ml of water was administered orally to the test group while the control group was given water (1ml).

After 30 min, 1.6g of soluble starch (40% solution/ 4ml) was administered orally to rats of both groups and the blood was collected directly afterwards (0min), 30 min, 1hr and 2hrs after the administration of starch. As shown in Fig. 8, the

elevation of blood glucose level was suppressed in the catechin group as compared to the control group. In the same way, the elevation of the levels of blood insulin and intestinal α-amylase concentration was suppressed [6].

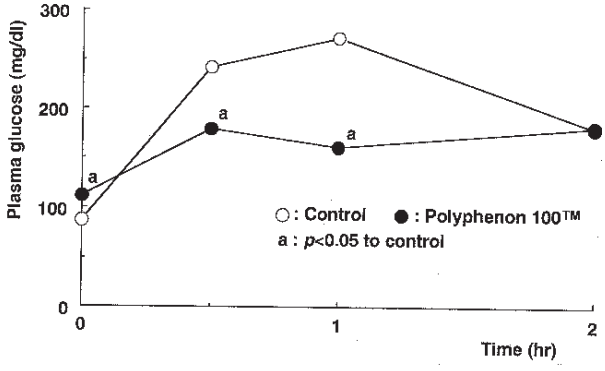

Fig. 8 Glucose concentrations in plasma of rats administered starch

Anti-microbial Action

At much lower concentrations than in a daily brew of green tea, catechins will inhibit the growth of foodborne pathogenic bacteria (Table 2) [7]. Tea catechins in particular EGCg were confirmed to interact with influenza virus and render the virus non-infective to cells. This was accomplished at a concentration as low as 3ppm (Fig. 9) [8]. These anti-microbial actions of tea catechins should be fully appreciated and utilized.

Bowel modulating Action

One hundred mg of tea catechins (160mg of "Polyphenon 60") were administered to bed-ridden inpatients at each meal, three times a day for three weeks. Their fecal specimens were collected at day 0, days 7, 14, 21 and one week after the finish of catechin administration (day 28). The analyses

Table 2 Minimum inhibitory concentrations of tea catechins against foodborne pathogenic and enteric bacteria

Bacteria	MIC (ppm)			
	EC	ECg	EGC	EGCg
Staphylococus aureus IAM 1011	> 800	800	150	250
Vibrio fluvialis JCM 3752	800	300	300	200
V. parahaemolyticus IFO 12711	800	500	300	200
V. metschnikovii IAM 1039	> 1000	> 1000	500	1000
Clostridium perfringens JCM 3816	> 1000	400	1000	300
C. botulinum A, B mix.	> 1000	200	300	> 100
Bacillus cereus JCM 2152	> 1000	600	> 1000	600
Plesiomonas shigelloides IID No. 3	700	100	200	100
Aeromonas sobria JCM 2139	> 1000	700	400	300
Lactobacillus brevis subsp. gravesensis JCM 1102	> 1000	> 1000	> 1000	> 1000
L. Brevis subsp. brevis JCM 1059	> 1000	> 1000	> 1000	> 1000
L. Brevis subsp. otakiensis JCM 1183	> 1000	> 1000	> 1000	> 1000
Bifidobacterium bifidum JMC 1255	> 1000	> 1000	> 1000	> 1000
B. adolescentis JCM 1275	> 1000	> 1000	> 1000	> 1000
B. longum JCM 1217	> 1000	> 1000	> 1000	> 1000

EC : (–) –cepicatechin, ECg : (–) –epicatechin gallate, EGC : (–) –epigallocatechin, EGCg : (–) –epigallocatechin gallate.

of the feces revealed a significant increase of lactic acid bacteria and a decrease of putrefactive bacteria as shown in Fig. 10. Othere fecal parameters also indicated very favorable improvement of intestinal conditions [9].

N.B. : "Polyphenon 100" used in various animal experiments has almost identical catechin content as "Polyphenon E" produced under cGMP which is now employed in Phase 2 trials against various human ailments.

Absorption of EGCg by oral administration to humans

A Phase I pharmacokinetic study to determine the systemic availability of green tea catechins after single oral dose administration of EGCg and Polyphenon E was conducted with twenty healthy subjects [10]. They were assigned to one of the dose levels (200, 400, 600, and 800 mg based on EGCg content). Blood and urine samples were collected for up to 24 hours after oral

Inhibition of the Influenza Virus by EGCg

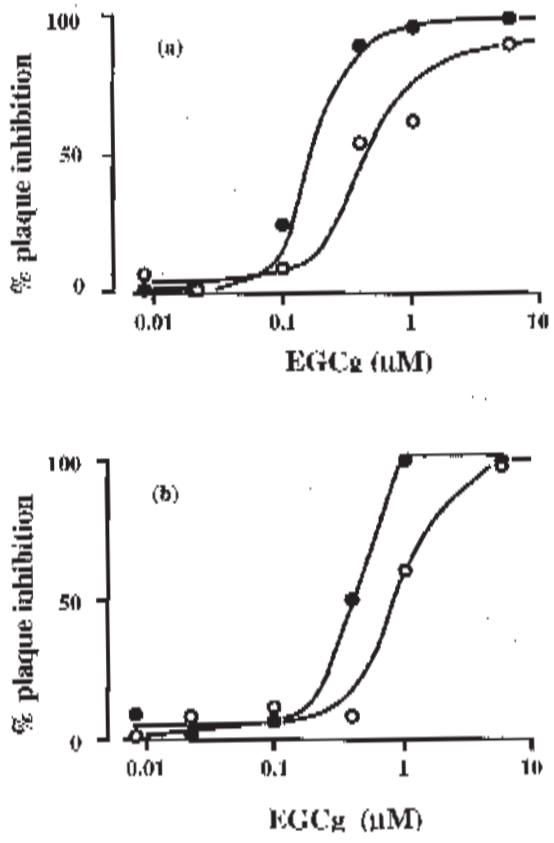

Fig. 9

Inhibitory effects of EGCg on plaque formation by influenza A virus (a) and B virus (b)

Influenza virus stocks were diluted to 2×10^3 p.f.u. ml^{-1} and incubated with various concentrations of EGCg for 5 min (○) or 60 min (●) at 37℃ before virus exposure to MDCK cells. The inhibition of plaque count was scored by the mean of triplicate cultures for each group after assay. Mean p.f.u. ±S.D. was 78.8±22.1 of control of eight experiments.

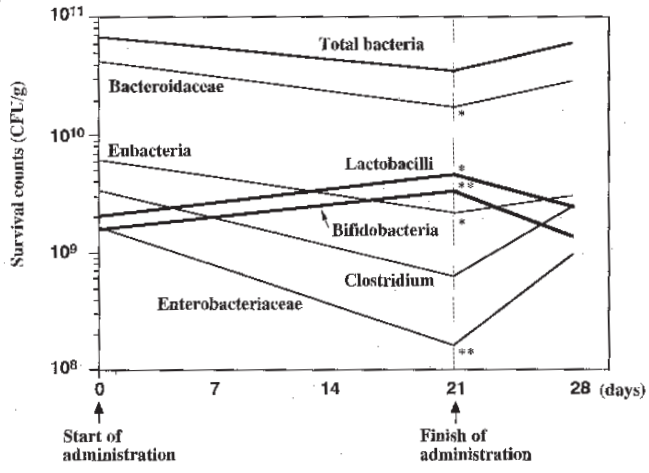

Fig 10. Effect of tea catechin administration on fecal flora of 15 human volunteers.
Graph is expressed as mean ± SD.
*,**;Significant difference (*p<0.05, **p<0.01) from the value of day 0 (before the administration).

administration. After EGCg versus Polyphenon E administration, the mean area under the plasma concentration-time curves (AUC) of unchanged EGCg were 22.5 versus 21.9, 35.4 versus 52.2, 101.9 versus 79.1, and 167.1 versus 161.4min-μg ml at the 200, 400, 600 and 800 mg dose levels respectively (Fig. 11). High concentrations of EGC and EC glucuronide/sulfate conjugates were found in plasma and urine samples after Polyphenon E administration. The AUC and maximum plasma concentration (Cmax) of EGCg after the 800mg dose of Polyphenon E were significantly higher than those after the three lower doses. We conclude that the two catechin formulations resulted in the similar plasma EGCg levels. The systemic availability of EGCg increased at higher doses, possibly due to saturble presystemic elimination of orally administered green tea polyphenols.

Conclusion

The isolation of tea catechins from green tea and the study of their physiological actions have been conducted extensively over the last 20 years. Several of the most notable actions of tea catechins have been dealt with here. Conclusively, tea catechins have the ability to fight against not only the chronic diseases to which people in affluent societies are by and large prone to, but also newly-or re-emerging infectious diseases which are likely to be the menace of humankind in the coming century. Not only are tea catechins effective, they also have some other superb merits.

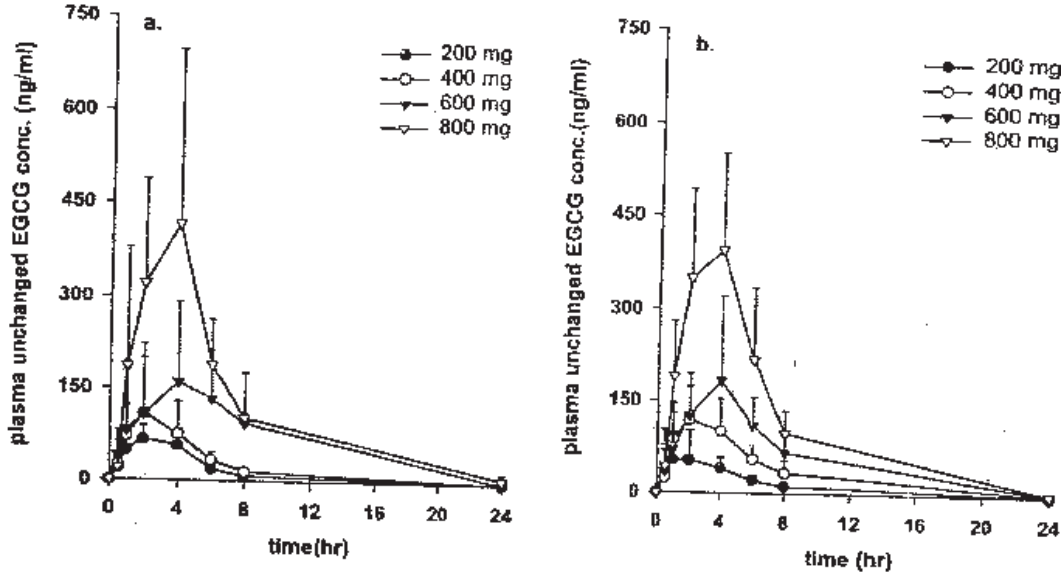

Fig 11. Average plasma EGCG concentration *versus* time profiles after oral administration of EGCG or Polyphenon E at different dose levels. a, EGCG formulation : *b,* Polyphenon E formulation. Each point represents the average of five subjects, and the *cross-vertical bars* represent 1 SD of the mean. ●, 200mg; O, 400 mg; t, 600mg ; ▽ 800mg.

They have been consumed by countless people for thousands of years, hence they have very high public acceptance. No toxicity has ever been ascribed to tea ie. tea catechins, or oligo-catechins in black tea and the adundance of these tea polyphenols in tea warrants their commercial feasibility. Recently, there have been increasing attempts to utilize tea catechin powder ("Polyphenon™s") in such products as dietary supplement capsules, catechin enriched soft drinks, low cholesterol eggs, candy, cosmetics, anti-flu filters, environmental odor adsorptiton filters, etc.

Above all, we are in the process of assigning tea catechins to Active Pharmaceutical Ingredients (API). Phase 1 studies have almost been completed with "Poltphenon E" which was produced under cGMP and various Phase 2 trials are under study, with particular emphasis on cancer chemoprevention. Thus, we are anticipating an age where a comprehensive catechin/Polyphenon™ industry will serve the health of people.

Reference

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