Elucidation of Physiological Functions of Tea Catechins and Their Practical Applications

YUKIHIKO HARA*

Tea Solutions, Hara Office Inc. Tokyo, Japan

ABSTRACT

In 1981, we found in collaboration with the late Dr. Tsuneo Kada that the compound in brewed green tea which suppresses the mutability of *Bacillus subtilis* is(-)-Epigallocatechin gallate(EGCg). Taking advantage of these findings, we started to isolate EGCg and other catechins in large amount from green tea for the first time in the world. We had made use of these samples, for ourselves and for our collaborators around the world, for the elucidation of physiological functions of tea catechins, under the assumption that the various so far claimed health benefits of tea drinking should have derived from tea catechins. From 1996 onward, we have been supplying the defined tea catechin mixture, Polyphenon® E to the US National Cancer Institute(NCI) for their chemoprevention clinical trials in over 20 instances. Separately, we found in 1990 that the topical application of tea catechins on genital warts caused by HPV eliminates the warts in a number of trials in Beijing Cancer Center. The results prompted a German pharmaceutical company to do the Phase 2/3 trials in EU and US. In 2006, the US FDA(Food and Drug Administration) approved the marketing of Polyphenon® E ointment, Veregen®, as the first "Botanical Drug" under FDA regulation. Currently, new developmental work with Theaphenon® E is underway.

Key words: tea catechins, Epigallocatechin gallate, EGCg, Polyphenon® E, Theaphenon® E, Botanical Drug

INTRODUCTION

Various beneficial health functions of tea catechins have been investigated over the last 30 years. Those representative properties and beneficial health effects were reviewed in two books by Hara[1] and Kuroda and Hara[2]. The topics include history of tea, catechins and their extraction methods, anti-oxidative action[3], anti-bacterial action[4] , anti-viral action[5] , prevention of cancer[6] , hypolipidemic action[7] , hypoglycemic action[8], hypotensive action[9] , effects on intestinal flora[10], and practical applications of those functions

Recently, very extensive reviews on "Tea and Health" were edited by CS Yang *et al.*[11,12], in which the habitual intake of tea catechins, with their very potent anti- oxidative, radical scavenging actions, is quoted to have a protective effects against such life-style-related, age-related diseases as cancer, cerebro, coronary diseases as well as the effects on the body weight or on bone health are discussed. Tea catechins also show very potent affinity with specific molecules, compounds or microbes, which imparts tea catechins with properties such as anti-viral and anti-bacterial actions against life threatening infectious diseases and deodorizing actions against oral or environmental odors. Recently, an entirely new function of EGCG against cancerous cells has been proposed by Tachibana, H. where the binding of EGCG to 67kD Laminin Receptor, specific to cancerous cells, triggers the apoptotic process[13]. In this review, recent developments in the application of tea catechins in the prevention and treatment of diseases and a trial for the wider use of tea are discussed.

PREVENTION OF CANCER

From the point of view of safety and public acceptability, chemoprevention by food or food ingredients seems to be a most welcome idea but no food or food ingredients have ever been approved by a Health Authority, such as the US or EU FDA, to be marketed as a chemoprevention drug.

In attempts to realize an approved drug for chemoprevention, the US NCI and we (Mitsui Norin Co. Ltd.) worked for more than 10 years from 1996, mainly on the safety of the intended agent[14]. We manufactured "Polyphenon® E", by extraction from green tea leaves (*Camellia sinensis*), which is composed of about 70% EGCg and the rest of other tea catechins[15]. In 2004 the US FDA issued a guideline for "Botanical Drug Products" wherein active components (Active Pharmaceutical Ingredient; API) of a botanical drug should be the crude extract of plants without being purified. The critical feature of a botanical drug is that no particular effective component is assumed[16]. The agent will be approved as a botanical compound if the defined crude extract in the drug formula shows efficacy in clinical phase trials. As a crude extract of green tea, Polyphenon® E is composed of more than 10 different catechins as well as other miscellaneous components including trace of unknowns.

In the manufacturing of Polyphenon® E under cGMP (current Good Manufacturing Practice) on the Botanical Drug system, certain criteria must be fulfilled in the

*Author for correspondence. Tel: +81-03-36268295;
Fax: +81-03-36268295; E-mail: ysjrhara@soleil.ocn.ne.jp

Table1. ***Clinical Trials.gov*** (Key word: Polyphenon E)

No	Study
1. (R)	Study of Polyphenon E in Men with High-grade Prostatic Intraepitherial Neoplasia (Phase 2) Sponsor: H.Lee Moffit Cancer Center and Research Institute
2. (C)	Erlotinib and Green Tea Extract(Polyphenon® E) in Preventing Cancer Recurrence in Former Smokers Who Have Undergone Surgery for Bladder Cancer (Phase 2) Sponsor: University of California, Los Angeles
3. (R)	Safety and Neuroprotective Effects of Polyphenon E in Multiple Sclerosis (Phase 2) Sponsor: National Center for Complementary and Alternative Medicine (NCCAM)
4. (R)	Study to Evaluate Safety and Toxicity of Polyphenon E in HIV-1-infected individuals (Phase 1) Sponsor: Baylon College of Medicine
5. (U)	Safety of Polyphnon E in Multiple Sclerosis Pilot Study (Phase 1) Sponsor: National Center for Complementary and Alternative Medicine (NCCAM)
6. (A)	Safety of Polyphenon E in Addition to Erlotinib in Advanced Non Small Cell Lung Cancer (Phase 1/2) Sponsor: Louisiana State University Health Science Center
7. (C)	Efficacy and Safety Study of Polyphenon E to Treat External Genital Warts (Phase 3) Sponsor: MediGene
8. (R)	Phase 1 Chemoprevention Trial With Green Tea Polyphenon E and Erlotinib in patients With Premalignant Lesions of the Head and Neck (Phase 1) Sponsor: Emory University
9. (A)	Green Tea Extract in Preventing Esophageal Cancer in Patients with Barrett's Esophagus (Phase 1) Sponsor: M.D. Anderson Cancer Center
10. (R)	Treatment of Epidermolysis Bullosa Dystrophica by Polyphenon E (Phase 2) Sponsor: Centre Hospitalier Universitair de Nice
11. (U)	Pilot Study of Green Tea Extract in Ulcerative Colitis (Phase 2) Sponsor: University of Louisville
12. (A)	Green Tea or Polyphenon E in Preventing Lung Cancer in Former Smokers With Chronic Obstructive Pulmonary Diseases (Phase 2) Sponsor: University of Arizona
13. (A)	A Study of the Effect of Polyphenon E on Breast Cancer Progression (Phase 2) Sponsor: Louisiana State University Health Science Center, Shreveport
14. (A)	Green Tea Extract in Treating Women With Homone Receptor-Negative Stage 1,2,3 Breast Cancer (Phase 1) Sponsor: M.D. Anderson Cancer Center
15.(C)	Green Tea Extract in Preventing Cancer in Healthy Participants (Phase 1) Sponsor: University of Arizona
16. (C)	Pharmacokinetic Study of Topically Applied Veregen 15% Compound With Oral intake of Green Tea Beverage (Phase 4) Sponsor: MediGene
17. (A)	Green Tea Extract in Treating Patients With Stage 0, 1,2 Chronic Lymphocytic Leukemia (Phase 1/2) Sponsor: Mayo Clinic
18. (S)	Defined Green Tea Catechin Extract in Treating Patients With Localized Prostate Cancer Undergoing Surgery (Phase 2) Sponsor: Case Comprehensive Cancer Center
19. (N)	Treatment of the Recessive Nonbullous Congenital Ichthyosis by the Epigallocatechin Cutaneous (Phase 4) Sponsor: Centre Hospitalier Universitaire de Nice

Table1. ***Clinical Trials.gov*** (Key word: Polyphenon E) (continued)

No	Study
20. (U)	Green Tea Extract in Treating Patients With Nonmetastatic Bladder Cancer (Phase 2) Sponsor: University of Wisconsin, Madison
21. (T)	Green Tea Extract in Treating Patients With Actinic Karatosis (Phase 2) Sponsor: University of California, Irvine
22. (R)	Green Tea Extract in Treating Current or Former Smokers With Bronchial Dysplasia (phase 2) Sponsor: British Columbia Cancer Agency
23. (C)	Green Tea Extract and Prostate Cancer (Phase 2) Sponsor: Louisiana State University Health Science Center, Shreveport
24. (T)	Green Tea Extract in Preventing Cervical Cancer in Patients With Human Papillomavirus and Low-Grade Cervical Intraepithelial Neoplasia (Phase 2) Sponsor: National Cancer Institute(NCI)
25. (R)	Green Tea Extract in Treating patients With Mono- clonal Gammopathy of Undermined Significance and/or Smoldering Multiple Myeloma (Phase 2) Sponsor: Barbara Ann Karmanos Cancer Institute
26. (R)	A pilot Study of Chemo-prevention of Green Tea in Women With Ductal Carcinoma in Situ (Phase 2) Sponsor: University of Chicago
27. (A)	Green Tea Extract in Preventing Cancer in Former and Current Heavy Smokers With Abnormal Sputum (Phase 2) Sponsor: British Columbia Cancer Agency
28. (C)	Defined Green Tea Catechins in Treating Patients With Prostate Cancer Undergoing Surgery to Remove the Prostate (Phase 1) Sponsor: National Cancer Institute (NCI)

(A): Active, not recruiting, (C): Completed, (N): Not yet recruiting, (R): Recruiting, (S): Suspended, (T): Terminated, (U): unknown

specification, such as “consistency”, “stability”, “absence of adulterants” and “traceability”. In other words, as an FDA official put it, “process is the product”. The huge document which supports the above specification is termed DMF (Drug Master File) and is filed with the FDA. In the last 10 years, NCI/DCP (Dept. of Chemoprevention) have been supporting more than 20 clinical phase 1 and 2 trials of chemoprevention, making use of Polyphenon® E capsules/ placebos, in the States in collaboration with investigators as well as Mitsui Norin Co.[17]. See the following Table 1. The difficulty in these trials is to identify biomarkers that accurately predict an agent’s clinical benefit or cancer-incidence reducing effect. Another difficulty is the recruiting of the subjects since those subjects are essentially healthy individuals with little motivation to join in the trials.

Since chemoprevention trials are very laborious and time/ money- consuming affairs with no assured results, it will be better to carry out a thorough feasibility study before launching them, in particular the business, commercial outlook and the risk/benefits thereof should be studied in depth.

On the other hand, if we continue with our present food grade status, with no clinical claims on the label by doing no clinical phase trials, we have to remain within the same regulatory framework as before in spite of all the evidence for possible clinical chemopreventive efficacy.

In order to overcome the above stalemate, I would like to propose the following measures to the health agencies which have no “Botanical Drug Guidelines”. First of all, to enact the regulation of “Botanical Drugs”. The active pharmaceutical ingredient should be the crude extract derived from plants. Secondly the agency should support the realization of Botanical Drugs and related processes financially, anticipating a world in which chemoprevention drugs will be available with firm scientific confirmation of the specific biomarkers.

AN FDA-APPROVED BOTANICAL DRUG

Here is a brief overview of our successful registration of a tea extract product with the US FDA. Along with the NCI projects, the development of a botanical drug was successfully completed in a certain clinical setting. Application of Polyphenon® E ointment on genital warts (*Condyloma acuminata*) caused by HPV (Human Papilloma Virus) removed the warts effectively in Beijing Cancer Center(Hospital) in 1990 in a fact finding trial. This is a therapeutic effect of tea catechins on benign tumors and the results were patented[18]. On this basis, a German pharmaceutical company spent time and money on Phase 2/3 clinical trials internationally. In 2006 the US FDA approved the marketing of the ointment as a prescribed Botanical Drug in the States under the trademark of “Veregen®”. This is the first ever Botanical Drug approved under the FDA Guideline, with no

subsequent approvals up until now[19].

On my retirement from Mitsui Norin Co., in 2008, I handed over to my successors the whole Polyphenon® world, which I had built up with my colleagues and collaborators over 30 years of efforts. Recently, I registered a new trade mark of "Theaphenon®" and started operations at my new venture, "Tea Solutions, Hara Office Inc." aiming to supply Theaphenon® E as well as EGCg and other catechins to the concerned.

ULTIMATE RTD TEAS

Currently, I am directing a national project in Japan to manage R&D for the Ultimate RTD (Ready-to-Drink) Teas of the world. I am of the belief that, in the years to come, the carbonated sugar drinks world-wide should be replaced, at least in part, by tea drinks of various efficacies with regards to health benefits. This idea, which anticipates several entirely new RTD tea drinks, was supported and was funded in 2009 by the National Science and Technology Agency (Japan) with 10 million USD over a five year period. The basic concept is to shed light by science on the traditional way of tea manufacturing , which I call it "Tea Renaissance". Teas manufactured and consumed today, green tea, black tea, oolong tea and others are the outcome of historical trials and errors by so many people in various regions. If we could control the actions of enzymes in tea by the radiation of certain wavelength or by addition of enzymes from external sources, we would be able to manufacture very different RTD teas that are more flavorful than present ones with certain marked health benefits.

In another 3 years, I am determined to convince several big beverage companies to take up the idea and go forward with commercialization of the Ultimate RTD Teas for the benefits of consumers as well as for that of beverage companies.

CONCLUSIONS

From my 40 years experience in tea and its R&D, as beverages or as a medicinal plant, I would say that there will be a huge possibility for tea to be a heath promoting material for every human body and much has to be researched to prove those efficacies and to elucidate the mechanisms thereof. A recent finding that there is a specific receptor protein of EGCg on the membrane of cancerous cells is very promising and warrants future clinical trials[13].

As regards botanicals other than tea , there should be many other natural plants or their ingredients to be a botanical drug. "Botanical Drug" is a nice idea of the US-FDA. If "crude extract" of tea is approved as a cancer preventive/curative agent, a great number of consumers would become heavy tea drinkers or buy tea capsules and that will reduce the cancer incidence to a certain extent. The government could reduce the huge medical expenditures by the pocket money of consumers for tea products. In the case of the tea catechin drug against genital warts, it unfortunately could not drive people into drinking more tea. I am sure that if a crude extract of a certain medicinal plant or a certain food ingredient works on a certain human disorder on a folklore basis or in animal experiments, there could be chances of this crude extract being approved as Botanical Drug if only chemically well defined, processed under cGMP with proven efficacy/safety in clinical phase trials. Separately, RTD teas are good carriers of various other herbs or medicinal plant extracts. In addition to the new RTD teas, combination of tea (*Camellia sinensis*) and those medicinal plants in RTD beverages should be pursued more extensively, aiming at their commercial production for people's good health.

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