

Tea and Cancer Prevention

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Abstract: Cancer remains one of the biggest challenges in the 21st century, therefore anti-cancer drugs and their delivery systems are under developing for better treatment. Tea is the amazing gift nature offered to us with great health benefits. Tea polyphenols especially EGCG and Theoflavins have widely been studied and expected to be a very promising nature polyphenol for the prevention of cancer, cardiology disease, aging, weight control etc. Here "Dr. Tea" summarized the past studies about tea and cancer prevention, through the chemical composition, structure, epidemiologic study and mechanism analysis. And based on the epidemiologic study results, a layer-by-layer multi-functional drug delivery system and synergy studies based on our past scientific working experience had been proposed for future tea and cancer research. A "Healthy, Harmony, Pure & Nature" tea-style of living is proposed for all human-beings towards a better living "self" and a better society.

Keywords: Tea, cancer prevention, Bohea Tea, polyphenol, drug delivery system, synergy, layer-by-layer, multi-functional, tea-style, "Dr. Tea", Healthy, Harmony, Pure and Nature.

CANCER AND CANCER TREATMENT

Cancer remains one of the most challenging diseases in the face of human-beings. In America, more than 1600 people die of cancer every day, accounting for one fourth of total deaths. More than 1,660,000 new cancer cases are diagnosed yearly. The NIH (National Institute of Health) estimated the yearly costs of cancer to be over 260 billion dollars. Traditional cancer treatments often have side effects of killing healthy cells and causing toxicity to patients [1-3].

Many natural derived polyphenol components (like curcumin [4-9] and tea polyphenols [10-18]) possess antioxidant and anticancer properties, which protect cells against the damaging effects of reactive oxygen species (ROS) and inhibit the signal induction and transcription of cancer cells [10-13]. Therefore, extensive studies had been carried out for tea and other nature products.

TEA HISTORY, BOHEA TEA AND MEDICINAL DRINK

Tea, originated from southern China, had been used as a medicinal drink since 3000 B.C. in the form of white tea and green tea later on. Tea is the largest beverage in the world second only to water and the most prevalent drink with lots of health benefits, including cancer prevention, that people can easily enjoy daily. Before 19th century, all teas consumed by the western society were produced in China, among which highest credits should be given to the Bohea

Tea. The Bohea Tea was widely known to be used for the treatment for the sickness of the Emperors' family. Black tea and Oolong tea were initiated developed in Fujian, China, especially in the Bohea mountain area, which is the world culture and nature heritage site by UNESCO (United Nations Educational, Scientific and Cultural Organization). The Bohea Tea is famous all over the world, being the Chinese Emperor's tea for thousand years and the main tea connecting the world history which is related directly to the Boston Tea Party, President Thomas Jefferson, President Richard Nixon, Premier Winston Churchill, Portuguese princess and British Queen etc. Swedish Botanist Carl Linnaeus wrote in his 《Species》 that tea can be divided into green tea and Bohea Tea. Even the word "tea" comes from the Fujianese dialect "te". As Dr. Xingcai Zhang ("Dr. Tea") said in his presentations at Harvard School of Public Health: "China is the only long-lasting continuous culture in the world, Bohea Tea is the materialistic, cultural and historical bridge connecting the past civilization and the modern world". The contribution of the Chinese, especially the Fujianese to the tea culture, tea history and tea science should be highly appraised and well-recognized.

Not only historically tea is widely used for medicinal purpose, more and more scientific health studies shaping people's view towards tea as the great treasure from nature. Many experimental studies have shown the anti-oxidant and anti-cancer effects of tea polyphenols. They are found to block various stages of carcinogenesis including cancer initiation, promotion and progression [10-13].

TEA AND TEA POLYPHENOLS

The health benefits of tea come from the synergy of various composition of tea, while tea polyphenols are

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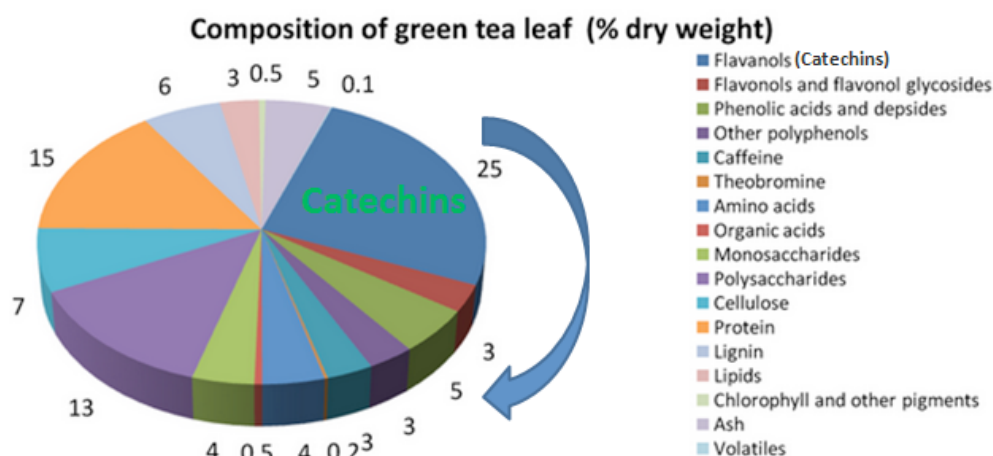


Figure 1: Main compositions of dry green tea leaves [11-12].

the main and most beneficial components of tea. The most widely studied tea polyphenols are green tea polyphenols, which are called catechins. The composition of a typical green tea leaf is shown in Figure 1 as adapted from reference [14-15]. The total catechins sum up to around 25% of the dry weight of green tea leaves. Among all catechins, EGCG is the most abundant (50-75%) and most effective.

GREEN TEA POLYPHENOLS (CATECHINS)

There are mainly 8 types of catechins as is shown in Figures 2 and 3, including 1: catechin (C), 2: gallocaetchin (GC), 3: catechin-3-gallate (CG), and 4: gallocaetchin-3-gallate (GCG) as is shown in Figure 2, and their corresponding isomers epicatechin (EC),

epigallocaetchin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) in Figure 3. The isomer with trans-configuration is called catechin and the one with cis-configuration is called epicatechin. The formation of catechin and epicatechin isomers is due to the two chiral centers of the two close-by carbons in the dihydropyranheterocycle ring with one of them being connected with a hydroxyl group.

Figures 2-3 shows the structure and relationship among different catechins, how they are forming the group of catechins and they are interconnected. Besides those different catechins, one very important polyphenol should be paid special attention to. That is the Gallic Acid (G).

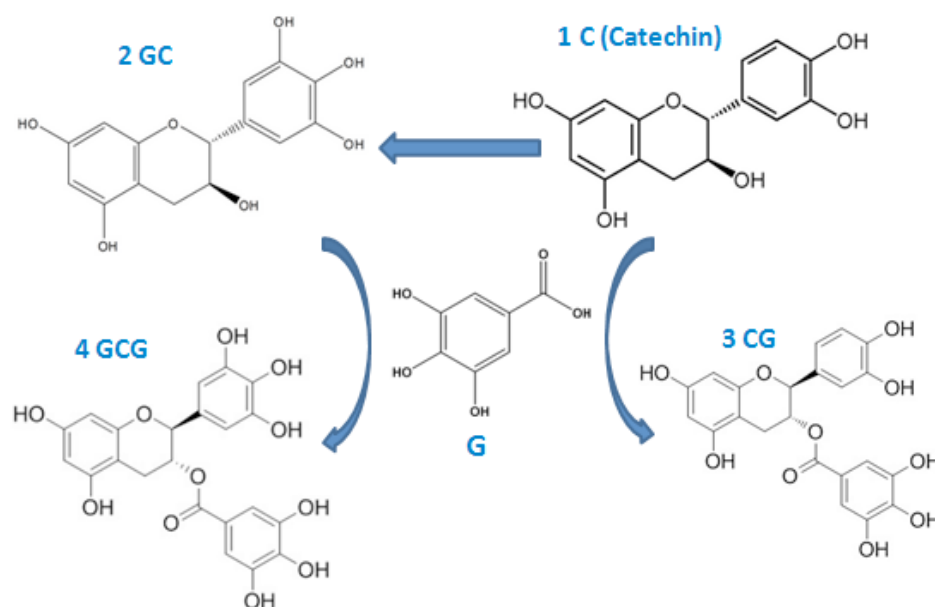


Figure 2: Four types of catechins, including 1) catechin, 2)(-)-gallocaetchin (GC), 3)(-)-Catechin gallate (CG), and 4) (-)-Gallocaetchin gallate (GCG). The precursor for CG and GCG is G, which stands for Gallic Acid [16].

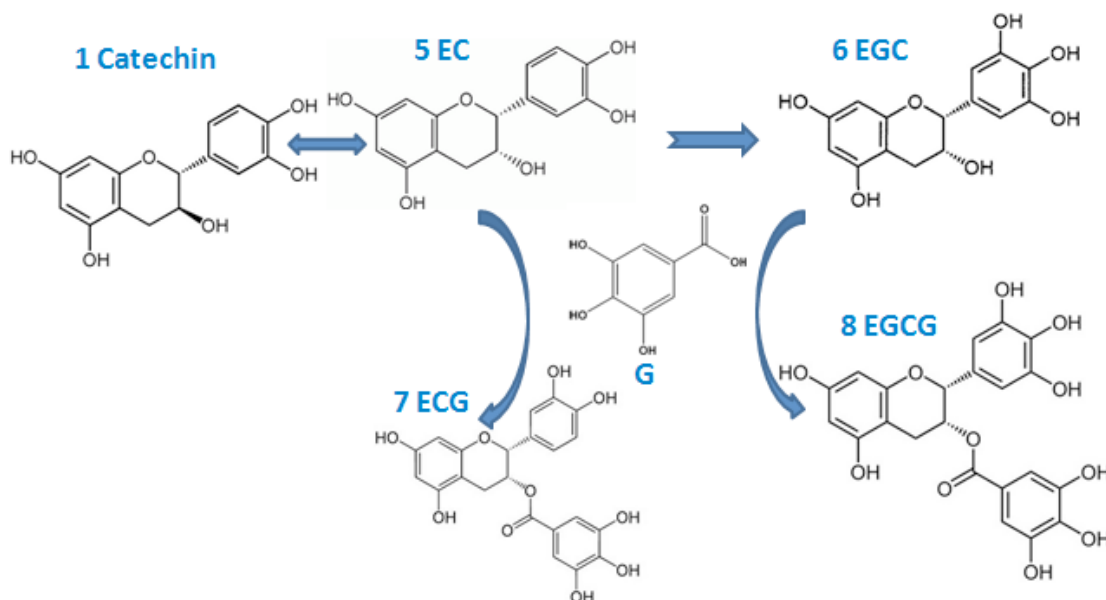


Figure 3: The other 4 types of catechins. They are the thermal isomers of the 4 types shown in Figure 2, including 5)(-)-epicatechin (EC), 6)(-)-epigallocatechin (EGC), 7)(-)-epicatechin gallate (ECG), and 8)(-)-epigallocatechin gallate (EGCG) [16].

The Gallic Acid (G) is the precursor for CG, GCG, ECG and EGCG. Research had found that the interaction with gallic acid significantly enhanced the anticancer ability of those catechins (C, GC, EC and EGC). The Gallic Acid is a phenolic acid polyphenol which account for 0.5- 1.4% of the dry content of green tea leaves. It, together with other phenolic acids like chlorogenic acid (0.3% dry weight) and theogallin (1-2% dry weight), contributes to the astringent taste of tea after interacting with other polyphenols especially those catechins [10, 17-18].

BLACK TEA AND OOLONG TEA POLYPHENOLS

Black tea and Oolong tea, which are originally developed from the Bohea Mountain of Fujian, China and then spread out the world, are created through the process of oxidative fermentation of those catechins and other polyphenols of appropriately picked fine teas, resulting in the development of long lasting good flavor, more yellowish and brownish in color, higher overall polyphenol contents and further health benefits. Through fermentation, tea polyphenols (including catechins) go through enzymatic and chemical oxidation to become polymerized theaflavins and thearubigins.

As can be seen in Figure 4 and Table 1, theaflavins (around 3 dry weight % in black tea) are dimeric tea polyphenols through the condensation reactions of gallated and ungallated catechins during fermentation. The four major theaflavins formed are theaflavin (TF1),

theaflavin-3-gallate (TF2a), theaflavin-3'-gallate (TF2b), and theaflavin-3,3'-digallate (TF3). However, most of theaflavins formed in black tea processing will go further to form polymeric thearubigins. Compared with catechins, theaflavins have more phenol groups, which would further enhance their antioxidant and anticancer properties. Studies had shown that theaflavins are more active than EGCG in inhibiting TPA-induced mice ear edema [10, 19].

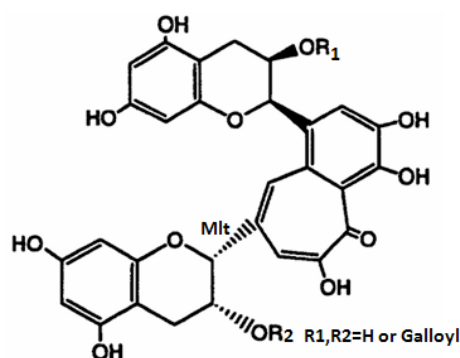


Figure 4: The chemical structure of Theaflavins [10].

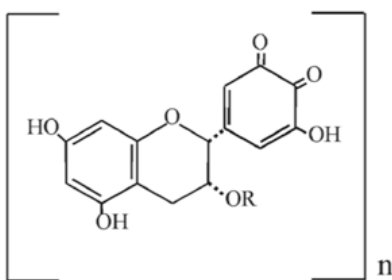
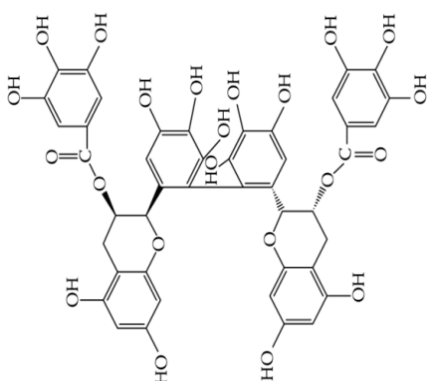
Black tea (i.e.: Lapsang Souchong, which is also called the Father of Black Tea) is considered to be the fully fermented tea in which thearubigins are the main fermentation products (10-20 dry weight %). Thearubigins are the further oxidized heterogeneous products of catechins and theaflavins with general MW (molecular weight) from around 1,000 to 40,000 Dalton. They are orange-brown in color and are difficult to separate for the study and understanding of their

Table 1: Theaflavins, Precursors, and Contents in Black Tea [10]

Theaflavins	TFs	Notation	R1	R2	Precursors	Content in Black tea (dry weight%)
Theaflavin	TF	TF1	H	H	EC.+.EGC	0.2-0.3%
Theaflavin-3-gallate	TF-3-G	TF2a	H	Galloyl	EC.+EGCG	1.0-1.5%
Theaflavin-3'-gallate	TF-3'-G	TF2b	Galloyl	H	ECG.+EGC	
Theaflavin-3, 3'-digallate	TF-3, 3'-DG	TF3	Galloyl	Galloyl	ECG.+EGCG	0.6-1.2%

structures, chemistry and bioactivities. MALDI-TOF spectra study of thearubigins showed similar yet more complicated polymers structures by further condensation reactions of GA, catechins and TFs [20]. Figure 5 shows a simplified structure for thearubigins [21].

Theasinesin A (Figure 6) is an oolong tea polyphenol whose structure had been confirmed by the synthesis through the free radical oxidation of the catechin EGCG. Oolong teas (i. e.: Health Goddess (Mother of Oolong Tea, Tie Guan Yin), Tea Pop (Father of Oolong Tea, Da Hong Pao)) are partially fermented tea in between black and green tea. Therefore they contain a mixture of catechins, theaflavins, and thearubigins. They are the richest in taste and aroma and acquire other benefits from both black and green tea.

**Figure 5:** Thearubigins [21].**Figure 6:** Theasinesin A [10].

ANTIOXIDANT PROPERTIES AND HEALTH BENEFITS

The antioxidant properties of tea polyphenols can inhibit (breast and prostate cancer etc) cell proliferation [10], regulate detoxifying enzymes [22], and induce cancer cell apoptosis [23], contributing to the beneficial effects of tea on a number of diseases related to reactive oxygen species (ROS), such as heart diseases, cancer, neurodegenerative diseases, aging, obesity and diabetes etc [14,24-31].

As we can see from the above structures, catechins are all natural antioxidant flavan-3-ols which have dihydroxylated (3,4-OH) and/or trihydroxylated (3,4,5-OH) benzene rings. The black and oolong tea polyphenols thus formed by fermentation have similar structure.

The main antioxidant sites of representative catechin (EGCG) and black/oolong tea polyphenol (Theaflavin) are shown in Figure 7. They are pretty much similar besides the fact that the benzotropolone skeleton of theaflavin can also be a participant during antioxidant reactions, which might make theaflavin an even better antioxidant than EGCG.

Those polyphenols, especially EGCG and theaflavins, can antioxidantize free radicals (superoxide, nitric oxide, hydrogen peroxide, nitrogen dioxide, hydroxyl radicals, singlet oxygen, peroxyxynitrite), chelate transitional metal ions (e.g.: Cu^{2+} , Fe^{3+}), and moderate certain biological systems like oxidant/antioxidant enzymes or genes which suppressed cancer proliferation through mitogenic signaling blockade etc. For transitional metal ions like Cu^{2+} and Fe^{3+} , Catechins may show prooxidant activity rather than antioxidant under certain conditions, which special attention should be paid to. By scavenging those radicals etc, polyphenols suppress radical chain reactions etc and terminate lipid peroxidation which may play important roles in carcinogenesis.

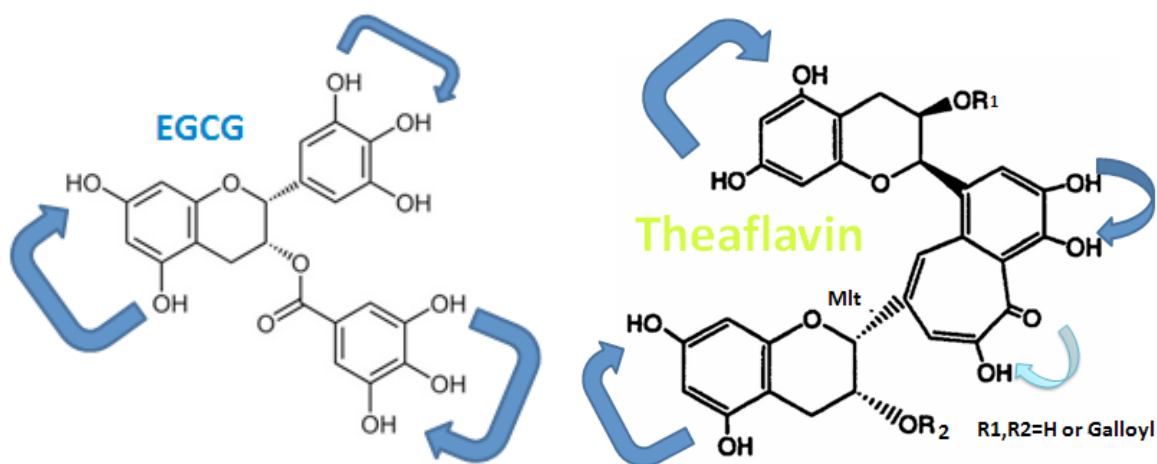
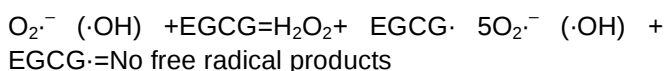


Figure 7: Anti-oxidative groups of EGCG and Theaflavin.

A case in point: as those arrows in Figure 7 have pointed out, EGCG can trap 6 superoxide anions ($O_2^{\cdot-}$) or ($\cdot OH$), while EC can only scavenge 2. The trapping mechanism of EGCG [10] is shown below:



PROPOSED CANCER CHEMOPREVENTION MECHANISMS

There are several mechanisms for the cancer chemoprevention effect of tea and tea polyphenols as is briefly summarized in Figure 8 [10]. Basically the antioxidant properties and the abilities of tea polyphenols to block the cancer cell proliferation signal pathways including carcinogenesis, invasion and

metastasis are the main reason for cancer prevention effects, based on the huge amount of research carried out. Figure 8 briefly summarized those pathways and how catechins, theaflavins and other tea polyphenols are working through to block those cancer cell proliferation pathways [10, 32-35].

EPIDEMIOLOGIC STUDIES AND DRUG DELIVERY SYSTEM (DDS) FOR TEA POLYPHENOLS

On one hand, tea, especially green tea is widely known for their cancer prevention effects. Especially in those animal models studied, tea polyphenols, including the most widely studied EGCG, have showed clearly the prevention effect against carcinogenesis in breast, colon, bladder, prostate, skin, lung, stomach, liver, small intestine, esophagus etc. [36,37].

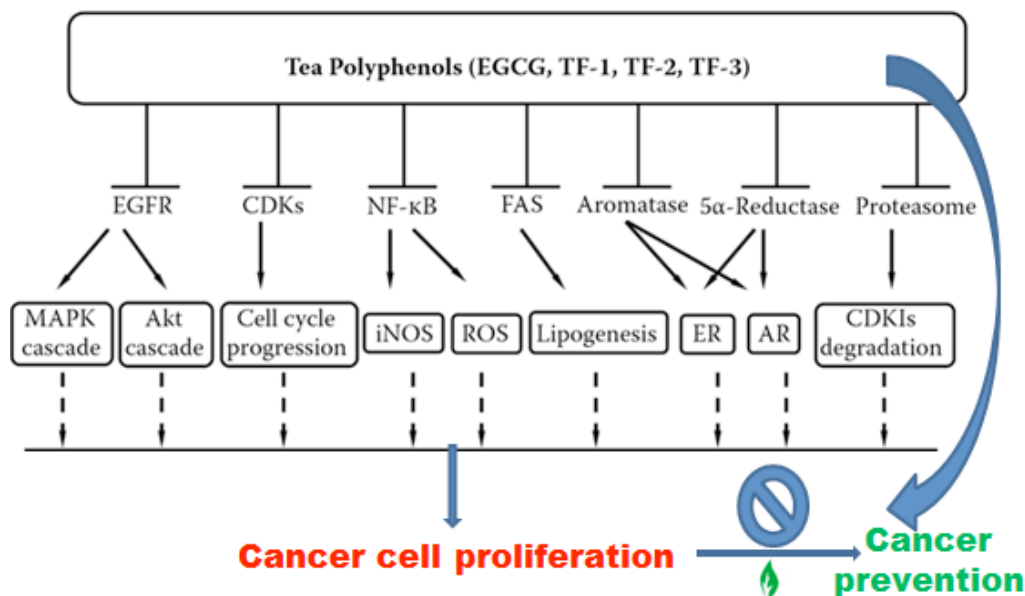


Figure 8: Proposed cancer chemoprevention mechanisms of tea polyphenols [10].

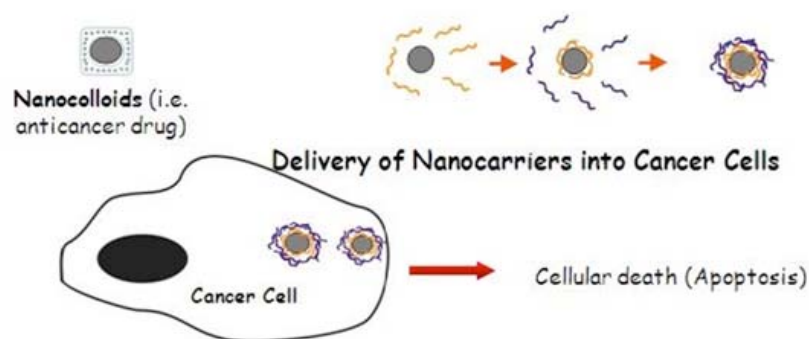


Figure 9: Methodology of Drug Delivery System for tea polyphenols [4].

However, on the other hand, the epidemiological study results of tea consumption on cancer prevention in humans have been inconsistent. Some case-control studies have shown an effect, like in the preventing of cancers in the digestive tract, especially the esophageal and gastric cancer [38]. Whereas some others studies do not show an effect [36].

Like curcumin [7-9], paclitaxel [39-41], lapatinib [40-41], and other efficient cancer drugs, those tea polyphenols are poorly soluble in water. Their bioavailability is low for human treatment, therefore, many epidemiological study results do not show a direct relationship between tea and cancer prevention.

Drug delivery systems (DDS) [7-9, 39-41] are designed to enhance the pharmacokinetics and therapeutic performance of drugs. Layer-by-Layer (LbL) self-assembly has been a well-established method for nanofabrication and nanoarchitecture build-up. LbL's versatility can be very useful for building up the drug delivery system. Here I suggest using the Layer-by-Layer (LbL) coating technology to establish a simple, effective method for preparing multifunctional tea polyphenol nanoparticles which can become stable, targeted releasable, traceable, aqueous and bioactive nanoparticles with high concentration (more than 70%) of the active tea polyphenol [3]. Using PEGylated polyelectrolytes for the self-assembly in the system can simultaneously achieve PEGylation for long time circulation and biocompatibility and biodegradability. Coating of antibody to the top of the DDS can achieve target delivery of the tea polyphenols into the specific site. Such a multi-functional system can pave the way for the solving of the inconsistent in the studies of tea consumption on cancer prevention. The detailed methodology is shown in Figure 9. The advantage of this methodology is that it can be applied to all those different polyphenols. The study on catechin (EGCG) and black/oolong tea polyphenol (Theaflavin) and oolong tea polyphenol Theasinesin as representative

tea polyphenols using this methodology will be of great importance in the future.

SYNERGY AND DUAL (MULTI-) DRUG DELIEVERY SYSTEM FOR TEA POLYPHENOLS

Our previous studies on different drugs [7-9, 39-41] and their combinations in one drug delivery system [39-40] show synergy. Results obtained by MTT test confirmed the enhanced cytotoxic activity of LbL-paclitaxel/lapatinib nanocolloids in P-gp overexpressing ovarian cancer cells compared to paclitaxel free and LbL- paclitaxel as is shown in Figure 10.

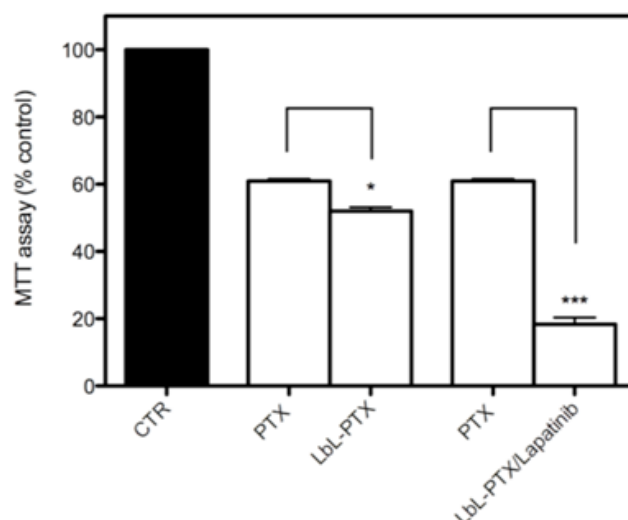


Figure 10: LbL-PTX/Lap nanocolloids demonstrate significant cytotoxic synergy as compared to PTX and LbL-PTX [4, 39].

Results obtained by MTT test confirmed the enhanced cytotoxic activity of LbL-paclitaxel/lapatinib nanocolloids in P-gp overexpressing ovarian cancer cells compared to Lapatinib as is shown in Figure 11.

Figures 10 and 11 shows the synergic effect of LbL-PTX/Lap nanocolloids for the enhanced cytotoxic activity over both the Paclitaxel and the Lapatinib.

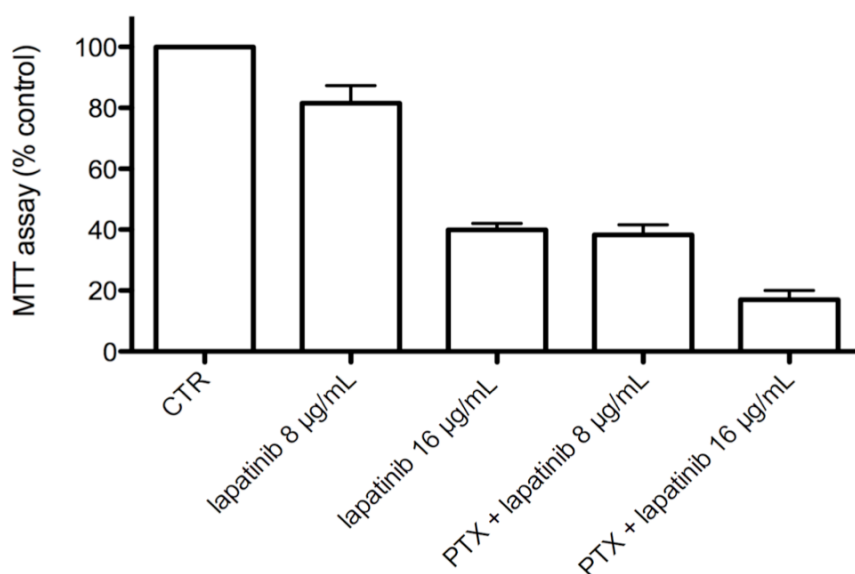


Figure 11: LbL-PTX/Lap nanocolloids demonstrate significant cytotoxic synergy as compared to LbL-Lapatinib [4, 39].

Other researches also show synergy on antioxidant effect among catechins, catechins with vitamin E [42], Sulindac [44], Tamoxifen [44], ascorbic acid [45] and Trolox [46] etc. Those synergy effects can be further improved using the DDS developed by our past work [39].

Using the layer-by-layer multifunctional (dual/multi-) DDS developed we proposed here and before [39] can pave the way for a better cancer prevention effect for tea polyphenols and the synergy of different polyphenols and other materials.

TEA: "HEALTHY, HARMONY, PURE & NATURE" LIFE-STYLE

Tea is a drink and more than a drink. Tea is a "Healthy, Harmony, Pure & Nature" life-style. As we go through the study of cancer prevention effects of tea and tea polyphenol, we find that tea and tea polyphenols are cancer preventive and tea polyphenols can be incorporated in the multi-functional drug delivery systems for effective cancer treatment. What is more important than that? Tea is a life-style, a culture of "Healthy, Harmony, Pure & Nature". Born in the beautiful nature, tea embraces the beauty and nutrition of nature, being in harmony with the environment and being very healthy and pure. Tea is the greatest treasure nature offered to us. The "Healthy, Harmony, Pure & Nature" tea-style is even more important than its cancer preventive effects and cancer treatment possibilities, due to the fact tea is a simple, healthy, easy to reach beauty we can enjoy from mouth, throat, heart to soul. The "Healthy,

Harmony, Pure & Nature" tea-style is a most cancer preventive, even more effective than the cancer preventative effect itself.

As a daily drink, tea can amuse and teach us how to enjoy and embrace the beauty of life at every single moment and bring us back to nature. Here, I, as a scientist and culture leader who was born in the best known home town of tea--Fujian, China, am sharing with everyone the culture, science, history and the Dao of tea: "Healthy, Harmony, Pure & Nature".

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Received on 30-01-2015

Accepted on 16-03-2015

Published on 07-05-2015

[DOI: http://dx.doi.org/10.6000/1929-2279.2015.04.02.4](http://dx.doi.org/10.6000/1929-2279.2015.04.02.4)