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Green Tea Polyphenols in drug discovery - a success or failure?

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Abstract

Green tea is made from unfermented dried leaves from *Camellia sinensis* and has been consumed by humans for thousands of years. For nearly as long, it has been used as a folk remedy for a wide array of diseases. More recently, a large number of in-vitro and in-vivo scientific studies have supported this ancient contention that the polyphenols from green tea can provide a number of health benefits. Since these compounds are clearly safe for human consumption and ubiquitous in the food supply, they are highly attractive as lead compounds for drug discovery programs. However, as drugs, they are far from optimum. They are relatively unstable, poorly absorbed, and readily undergo a number of metabolic transformations by intestinal microbiota and human enzymes. Further, since these compounds target a wide array of biological systems, *in-vivo* testing is rather difficult since effects on alternative pathways need to be carefully eliminated. The purpose of this review is to discuss some of the challenges and benefits of pursuing this family of compounds for drug discovery.

1. Introduction

Green tea is a significant source of a type of flavonoids called catechins (Figure 1): including epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). One 200 ml cup of green tea supplies 140, 65, 28, and 17 mg of these polyphenols, respectively ¹. There has been growing interest in EGCG since it has been suggested to decrease cholesterol levels ², act as an antibiotic (e.g. ^{3, 4}) and anticarcinogen (e.g. ^{5, 6}, repress hepatic glucose production ⁷, and may enhance insulin action ^{8, 9}. The exact mechanism of action of EGCG with regard to a number of these effects is not entirely clear. There continues to be a strong interest in clinical applications for these compounds as demonstrated by the fact that there are currently over 37 active clinical trials involving EGCG.

1.1 EGCG undergoes rapid auto-oxidation in solution

One significant problem with the tea catechins is their reactivity and instability under physiological and experimental conditions. Polyphenols such as the tea catechins are effective scavengers for superoxide anion radicals ($O_2^{\bullet-}$) and hydroxyl radicals ($OH^{\bullet}$). However, catechins themselves are easily oxidized by dioxygen that can produce active oxygen species such as hydrogen peroxide (H_2O_2) and $O_2^{\bullet-}$. Cupric ions (Cu^{2+}) exacerbate autoxidation and can also yield some potentially cytotoxic quinones as side products. Previous studies have shown that the first step of this autoxidation is the one-electron oxidation of the catechins to generate an $O_2^{\bullet-}$ and a semiquinone that effectively quenched by

Declaration of Interest

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H⁺ and superoxide dismutase¹⁰. However, the scavenging of the H₂O₂ *in-vivo* would require peroxidase or catalase since it reacts poorly with the catechins.

This reactivity can complicate *in-vitro* studies since EGCG has a half-life of less than 30 minutes in common cell culture media¹¹. EGCG forms dimers with a maximum at 30–60 min but then all monomeric and dimeric species disappear within six hours¹². Polymerization is superoxide-mediated and since superoxide dismutase (SOD) stabilizes EGCG. However, when SOD is added, an appreciable amount of epimerized EGCG, GCG, is formed. Some of these reactions may occur more slowly in tissue since the partial pressure of oxygen is ~1/4 that of cell culture and animal tissue has high levels of SOD, glutathione, and ascorbic acid¹². It is important to also note that during EGCG oxidation, phenolic radicals, superoxide radicals, and hydrogen peroxide can be formed. These oxidation side products can themselves trigger a number of cellular responses. For example, the effects of EGCG on epidermal growth factor receptor (EGFR) phosphorylation was abrogated by the addition of SOD, suggesting that in this case it was the side products of EGCG oxidation rather than EGCG itself that was inducing the cellular effect¹³.

1.2 EGCG is rapidly metabolized in-vivo

One major problem with the polyphenols is that they are poorly absorbed when administered orally. Their high solubility makes for poor membrane permeability and their reactive nature makes them unstable in the gut. Gut microbes also cause extensive degradation. Finally, there is significant efflux from these polyphenolic compounds from cells¹⁴. For a detailed review, see Feng, 2006¹⁵. Once absorbed, EGCG, like other polyphenols, is modified by sulfation, glucuronidation, and methylation before catabolism and excretion. Rats have the shortest serum half-life for EGCG while mice and humans are essentially the same. However, it has been suggested that EGCG in the serum is mostly unconjugated in humans¹⁶ while it is mostly in the conjugated form in mice¹⁷. Glucuronidation greatly increases the clearance rate from the serum. There have been numerous studies examining the pharmacokinetics of EGCG in mice, rats, and humans (For a review see¹⁸). In mice, more than a third of the administered EGCG is excreted in feces in the first 24 hours¹⁹. The level of EGCG found in the major organs was found to be ~1/10 that found in the serum. Most interestingly, this includes the brain, suggesting that EGCG passes through the blood-brain barrier. There have been a number of studies on the pharmacokinetics of these polyphenols in humans (e.g.^{16, 20–23}). In general, EGCG and EGC are absorbed at levels of 0.2–2.0% and 0.2–1.3%, respectively. This absorption efficacy is essentially the same whether administered as purified compounds or as a mixture (i.e. Polyphenon E)²⁴. EGCG is methylated *in-vivo* by human liver cytosolic catechol-O-methyltransferase (COMT)²⁵ that can negate at least some of its activity (e.g.²⁶). Interestingly, it has been reported that lower COMT activity in individuals correlates with more efficacious protection against breast cancer afforded by green tea extracts²⁷.

With regard to both the auto-oxidation and the *in-vivo* modifications, acetylation of the phenolic alcohol groups may be very useful in the pharmacological application of the tea catechins. Perhaps the most famous example of this is the acetylation of salicylic acid with acetic anhydride to form aspirin. This modification makes the compounds more hydrophobic and helps to block phase II biotransformation or oxidative degradation²⁸. Acetylated EGCG is deacetylated once taken up by various cell lines and studies on intragastric administration of acetylated EGCG showed that modification increased serum levels of EGCG 2.8–4.3 fold with an increased the half-life in the intestinal tract by 4–6 fold²⁹.

1.3 Tea polyphenols target a wide array of biological systems

There have been numerous potential therapeutic targets identified for the tea polyphenols. For brevity, only some of those with IC_{50} 's in the submicromolar range will be noted here. Tea polyphenols inhibit several proteases including matrix metalloproteinases (2, 9 and 12; ³⁰) and the 20S proteasome ³¹. The former has implications in tumor invasion and metastasis and the latter in tumor apoptosis. Tea catechins have been shown to inhibit dihydrofolate reductase much like the antineoplastic drug methotrexate ³². With possible implications for the control of serum cholesterol, EGCG has been shown to be a potent inhibitor of squalene epoxidase ³³. EGCG is not only modified *in-vivo* by human liver cytosolic catechol-O-methyltransferase, but is also a potent inhibitor of the enzyme ²⁵. Relatively few structures of enzymes complexed with tea catechins have been determined (e.g. 1JNQ, 3NG5, and 2KDH). In the case of troponin C ³⁴ and transthyretin ³⁵, EGCG binds at protein-protein interfaces. All of these studies clearly demonstrate that, even though EGCG is a strong antioxidant, and can affect such a wide array of cellular systems, its interactions with a particular enzyme can be highly specific and independent of its inherent chemical activity. It should be noted, however, that sometimes the diverse activity of green tea polyphenols can be deleterious. For example, the polyphenols have been shown to block the anticancer effects of several chemotherapy agent ³⁶. In spite of this, tea catechins, are often ignored in high throughput screens since the dogma is that they act by aggregating or denaturing target proteins.

1.4 EGCG as an inhibitor for glutamate dehydrogenase (GDH)

Our work has shown that EGCG has potential as an inhibitor of glutamate dehydrogenase activity. Hyperinsulinemia/hyperammonemia (HHS) is a genetic hypoglycemic disorder caused by loss of GTP inhibition ³⁷. This loss of GTP regulation results in profound effects on several major organs. In the pancreas, afflicted children have increased β -cell responsiveness to leucine and susceptibility to hypoglycemia following high protein meals ³⁸. This is likely due to uncontrolled catabolism of amino acids yielding high ATP levels that stimulate insulin secretion, causing severe hypoglycemia. In the liver and/or the kidneys, the hyperactive GDH catabolyzes glutamate, producing excessive ammonium. This hyperammonemia is further exacerbated by low glutamate concentrations that decrease N-acetyl-glutamate production that is a necessary activator for carbamoylphosphate synthetase (CPS) for ureagenesis. While the hypoglycemia and hyperammonemia in HHS are sufficient to cause CNS damage, afflicted children have higher incidence of childhood-onset epilepsy, learning disabilities, and seizures independent of the hyperammonemia and hypoglycemia ³⁹. This is likely due to the importance of glutamate and γ -aminobutyric acid as neurotransmitters. HHS is currently treated by pharmaceutically controlling insulin secretion but this does not address the liver and CNS problems. Therefore, there is a significant need for a new inhibitor to directly block hyperactive HHS GDH.

Of the four major catechins found in green tea, only ECG and EGCG showed inhibitory activity against GDH (Figure 1). EGCG and ECG allosterically inhibit purified animal GDH *in-vitro* with an ED_{50} ~500nM. Since EC or EGC were not active against GDH, the antioxidant property of these catechins cannot be relevant to GDH inhibition. Further, none of these compounds aggregated or irreversibly denature the enzyme ⁴⁰. Interestingly, ECG/EGCG inhibition complements the normal regulation of GDH. We have proposed that GDH is normally held in a 'tonic' state ⁴¹ where the preferred metabolism of carbohydrates and fats maintains a high GTP concentration in the mitochondria, thereby keeping GDH activity at a low level. GTP inhibition is released as the energy level drops and ADP concentrations rise. Similarly, ECG/EGCG inhibition is also abrogated by ADP ⁴⁰. Therefore, the green tea polyphenols are likely not toxic to a normal individual since the 'pressure release valve', ADP, can overcome EGCG/ECG inhibition if the energy of the mitochondria drops to very

low levels. Finally, with regard to application for HHS, EGCG inhibits HHS GDH mutants as effectively as wild type⁴⁰.

The next step was to ascertain EGCG activity in tissue (Figure 2). Mirroring what was found with purified enzyme, EGCG, but not EGC, blocked the GDH-mediated stimulation of insulin secretion by the β -cells. EGCG does not affect insulin secretion, glucose oxidation, or cellular respiration during glucose stimulation where GDH is known to not play a major role in the regulation of insulin secretion⁴⁰. In unpublished results, we have determined the structure of GDH complexed with EGCG and ongoing *in-vivo* studies on transgenic HHS mice are showing promise.

More recent studies have confirmed our observation that EGCG inhibits GDH *in-situ* and it may be useful in treating other diseases as well. The phosphatidylinositol 3'-kinase/Akt pathway is enhanced in many human tumors and up-regulates glucose uptake and utilization. c-Myc, on the other hand, up-regulates glutamine utilization by increasing cell surface transporters and enzymes. At least *in-vitro*, the enhanced utilization of one of these carbon sources also makes the cells sensitive to its withdrawal. Using our results, DeBerardinis laboratory tested the effects of EGCG on glioblastoma cells. They demonstrated that EGCG sensitizes glioblastoma cells to glucose withdrawal and to inhibitors of Akt signaling and glycolysis⁴². Indeed, EGCG addition mirrored the effects of knocking out GDH in the tissue.

Work from the Blenis group⁴³ also demonstrated EGCG inhibition of GDH activity may be useful in treating the tuberous sclerosis complex (TSC) disorder. The TSC disorder is characterized by benign tumors due to the loss of either TSC1 or TSC2 and the subsequent hyperactivation of the mammalian target of rapamycin (mTOR). Inhibitors of mTOR can decrease the size of TSC associated tumors, but only in a cytostatic manner. The TSC1/2 $-/-$ cells are hypersensitive to glucose deprivation and highly dependent on GDH mediated catabolism of glutamine. Nearly all of the TSC1/2 $-/-$ cells that were deprived of glucose and given rapamycin died upon administration of EGCG. As expected, EGCG effects was reversed if GDH mediated oxidation of glutamate was circumvented by the addition of 2-oxoglutarate, pyruvate, or aminooxyacetate. This is an exciting result since attempts to make glutamine analogs have only yielded toxic compounds.

2. Expert Opinion

It is clear that there are a number of interesting possible pharmaceutical applications for green tea catechins. However, there are a number of practical and scientific issues that are yet to be resolved. What is particularly attractive about these compounds is that are safe at very high doses. Once shown to be active against a particular target, it is logical to hope that one might expect to be able to move to clinical trials relatively quickly. Certainly, the low toxicity is highly advantageous in being able to rapidly test *in-situ* and in animal models. However, there are a number of issues that impede using the catechins as pharmaceuticals. These highly soluble and reactive compounds are poorly absorbed in the gut and quickly eliminated by the liver. This can only be partially compensated by administering larger doses of material. On the more practical side, the wide array of targets makes it difficult to demonstrate a specific mode of action and to obtain approval for a particular use. In addition, the large number of false starts in their application has jaded the community. Pharmaceutical companies are similarly skeptical, with the added problem in that it is nearly impossible to protect the application of such freely available compounds from patent challenges. These issues have certainly plagued our work on using EGCG to treat HHS. Since HHS is an orphan disease, we had hoped that such a non-toxic compound could be rapidly used in the clinic to help treat this multi-organ disease. However, for all of these

reasons, being able to get support for this application has been difficult. Nevertheless, in unpublished results, we have the atomic structure of the GDH/EGCG complex and evidence that they are working *in-vivo* in HHS transgenic mouse models. Therefore, we still are hopeful that either these compounds or their mimics might still be applicable for a number of diseases.

Whether the green tea polyphenols can be considered to be a success or failure is dependent upon whether the end application is a nutritional additive or a traditional pharmaceutical with a specific target and dosing regime. With regard to their use as a nutraceutical, a number of studies have suggested that they may be effective as prophylactics or as synergistic compounds with other treatment regimes. Used in this manner, these compounds have offered modest benefits with a number of different disorders. As pharmaceutical agents, these compounds have been highly successful in controlled experiments but have not resulted in clinical application. Tea polyphenols hold such great promise with regard to safety and ability to cross the blood-brain barrier. However, even with modifications to make them more stable pro-drugs, it seems unlikely that the stability and bioavailability issues can be sufficiently overcome. Therefore, as use as targeted pharmaceutical agents, these polyphenols cannot be considered a success at this time. However, they have been extremely useful in identifying new ligand binding sites on target proteins and their low toxicity allows for rapid confirmation of activity *in-situ* and *in-vivo*. In the end, perhaps this is how these catechins have lived up to expectations; by providing scaffolds for further drug design.

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Tea Polyphenols

Figure 1.

Structure of the four major polyphenols found in green tea. Also noted are the EC_{50} values for inhibition of purified GDH.

Figure 2.

Effects of EGCG and EGC on GDH-mediated secretion of insulin from pancreatic β -cells in a perfusion assay. EGCG clearly blocks GDH-mediated, BCH stimulation of insulin secretion in a dose-dependent manner. Importantly, EGC, which was shown to be inactive against purified GDH, has no effect on insulin secretion. Figure adapted from Li, et al.⁴⁰ by permission of the Journal of Biological Chemistry.