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Molecules of Interest

Epigallocatechin-3-gallate (EGCG): Chemical and biomedical perspectives

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Abstract

The compound (−)-epigallocatechin-3-gallate (EGCG) is the major catechin found in green tea [*Camellia sinensis* L. Ktze. (Theaceae)]. This polyphenolic compound and several related catechins are believed to be responsible for the health benefits associated with the consumption of green tea. The potential health benefits ascribed to green tea and EGCG include antioxidant effects, cancer chemoprevention, improving cardiovascular health, enhancing weight loss, protecting the skin from the damage caused by ionizing radiation, and others. The compound EGCG has been shown to regulate dozens of disease-specific molecular targets. Many of these molecular targets are only affected by concentrations of EGCG that are far above the levels achieved by either drinking green tea or consuming moderate doses of green tea extract-based dietary supplements. In spite of this, well-designed double-blinded controlled clinical studies have recently demonstrated the efficacy of green tea extracts and purified EGCG products in patients. Therefore, this review highlights results from what the authors believe to be some of the most clinically significant recent studies and describes current developments in the stereoselective total synthesis of EGCG.

Keywords: *Camellia sinensis*; Green tea; Catechins; Flavonols; Epigallocatechin-3-gallate; EGCG; Clinical trials; Cancer chemoprevention

1. Introduction

The natural product (−)-epigallocatechin-3-gallate (EGCG, **16**) is the major polyphenolic constituent found in green tea [dried fresh leaves of the plant *Camellia sinensis* L. Ktze. (Theaceae)] (Bettuzzi et al., 2006; Demeule et al., 2002). Several other polyphenolic compounds known as catechins are also found in lower abundance in green tea. These other catechins include (−)-epicatechin-3-gallate (ECG), (−)-epigallocatechin (EGC), (−)-epicatechin (EC) and (+)-catechin. More than 50% of the mass of this catechin combination is composed of EGCG and a vast body of scientific research suggests that EGCG (and other catechins) is responsible for the majority of the potential health benefits attributed to green tea consumption.

A recent search of the literature revealed more than 8000 citations that relate to the chemistry, bioactivity, production, and potential health benefits of green tea. Of these, over 4000 references pertain to EGCG and other natural products found in green tea (SciFinder, 2006). These citations can be classified into the following categories: (1) chemical analysis or characterization of green tea components; (2) epidemiological reports of various populations

Abbreviations: AD, asymmetric dihydroxylation; AIBN, 2,2'-azobis (isobutyronitrile); DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, dimethylaminopyridine; EC, (−)-epicatechin; ECG, (−)-epicatechin-3-gallate; EGC, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; GTC, green tea catechin; GTE, green tea extract; HG-PIN, high-grade prostate intraepithelial neoplasia; HPV, human papilloma virus; MED, minimal erythema dose; PPTS, pyridinium *p*-toluenesulfonate; rt, room temperature; TBDMSCl, tert-butyldimethylsilyl chloride; THF, tetrahydrofuran.

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that consume green tea products; (3) evaluations of the antioxidant effects of green tea catechins; (4) examinations of the biomedical potential of green tea components using *in vitro* models; (5) biochemical studies that investigate the effects of green tea catechins on specific enzymes and biochemical systems that are believed to be potential molecular targets for various diseases and chemoprevention; (6) patents on the methods of preparation or utility of green tea and EGCG products; (7) a relatively small number of investigations that have documented the *in vivo* health-promoting potential of green tea extracts or purified compounds using animal models; and (8) emerging reports on the potential health benefits of EGCG from well-controlled and double-blinded clinical studies.

There remain several major challenges to interpret the clinical relevance of the hundreds of studies that examine the effects of EGCG on various *in vitro* disease-related molecular targets and *in vivo* models for potential health benefits. The overwhelming majority of *in vitro* studies find that EGCG inhibits a vast array of biomedically relevant molecular targets and disease-related cellular processes at relatively high concentrations (reviewed in: Boik, 2001; Doss et al., 2005; Adhami et al., 2003; Haslam, 1996; Khan et al., 2006; Conney, 2003). These include *in vitro* anticancer molecular targets and tumor cell cytotoxicity studies conducted at test concentrations that typically range from about 10 to 1000 μM. By contrast, a relatively small number of studies have shown that EGCG can inhibit certain biomedically important molecular targets such as DNA methyltransferases (Lee et al., 2005), squalene epoxidase (Abe et al., 2000), antiapoptotic Bcl-2 proteins (Leone et al., 2003), and vascular endothelial growth factor receptor (VEGFR) signaling (Lamy et al., 2002) at sub-micromolar concentrations. Pharmacokinetic studies conducted in humans indicate that the physiologically relevant serum concentrations of EGCG may be in the high nanomolar range (Henning et al., 2004; Chow et al., 2003; Ullmann et al., 2003). Therefore, high micromolar concentrations are unlikely to be established in the bloodstream of individuals that simply drink green tea or ingest only two to three 200 mg capsules of green tea extract (GTE) each day. Yet, epidemiological studies continue to suggest that there may be significant health benefits associated with drinking green tea (Bushman, 1998). This is further supported by animal studies that indicate the consumption of green tea and green tea products with high levels of EGCG and other catechins may have a significant effect on the prevention of tumors, cardiovascular disease, and other medical conditions. Meanwhile, considerable speculation has arisen to "fit" the results from *in vitro* studies that demonstrate the activities of EGCG on most of the molecular-targets and the tumor cell cytotoxic effects exerted by EGCG and GTE at concentrations that are far above the physiologically relevant range. This apparent discrepancy has brought forth a number of possible explanations. It has been suggested that the effects of EGCG may be more synergistic when combined with other catechins than previously thought (Suganuma et al., 1999). It is also believed that EGCG (and other tea catechins) may be metabolically activated to form more potent and effective bioactive compounds. Others speculate that EGCG may accumulate in tissues over time to produce cellular concentrations that are much higher than those have been observed in clinical serum samples. Alternatively, the simplest explanation is that the effects of EGCG on many of its reported molecular targets are merely high-concentration effects or experimental artifacts that reflect the propensity of catechins and other polyphenolic substances to chelate metals and bind proteins in a nonselective manner (reviewed in Haslam, 1996). This is the main reason that the high-throughput pharmaceutical screening community has considered polyphenols and other tannins to be "nuisance" compounds that must either be removed from test samples or dereplicated prior to extensive evaluation in protein-based bioassay systems (i.e., enzyme or receptor) (Cardellina et al., 1993). If this is the case, only a relatively small number of the numerous molecular mechanistic studies reported for EGCG and other green tea products actually reflect physiologically relevant processes.

It is conceivable that many of the effects observed with micromolar concentrations of EGCG are relevant to the potential benefits, side effects, and/or toxicity of either high-dose or mega-dose GTE and EGCG therapy (Pisters et al., 2001; Zhou et al., 2004). Likewise, the tumor cell-specific cytotoxic effects produced by high micromolar concentrations of EGCG may not represent phenomena that are physiologically relevant to dietary green tea consumption, but may be indicative of effects that may be achieved with high-dose supplementation of EGCG and other catechins. For these reasons, the authors have selected not to discuss many aspects of EGCG research that have been summarized elsewhere (Doss et al., 2005; Adhami et al., 2003; Haslam, 1996; Khan et al., 2006; Conney, 2003).

It is not the intention of the authors to provide a comprehensive coverage of the immense body of EGCG research, nor is the objective of this review to summarize the large number of different areas of EGCG research currently taking place. The authors simply desire to describe current developments in EGCG catechin chemistry and discuss the results from what the authors believe to be some of the most clinically significant recent studies. A number of recently published clinical efficacy studies have been conducted with purified EGCG and various products that contain EGCG (i.e., various regular and decaffeinated green tea extracts). Some of these have been well-designed double-blinded and properly controlled studies. The authors have selected not to include those studies that lack appropriate controls or where there is no means to differentiate between the specific effects of EGCG and the effects of caffeine in green tea extract products.