P-038 **Micro and nanoencapsulation of EGCG for chemoprevention and co-therapy of colorectal cancer (Review)**

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INTRODUCTION AND OBJECTIVES

Colorectal cancer incidence continues increasing in the Western countries and if precocious diagnosis favors the survival of the affected ones, the rate of mortality is still high. In most people, this cancer develops slowly over several years. Overall, the lifetime risk of developing colorectal cancer is about 1 in 20 (5.1%) (American Cancer Society 2011). Hence, a growing amount of scientific research has been focused on the development of complementary strategies, such as chemoprevention to prevent the development of cancer and to reduce morbidity and mortality from colorectal cancer. Non-toxic bioactive food components, such as green tea polyphenols, have been shown to aid in the prevention and adjuvant treatment of colorectal cancer.

This review summarizes the potential chemopreventive potential of epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea, and discusses the role o micro and nano encapsulation on its efficacy and stability.

Tea (*Camellia sinensis*) is consumed worldwide and is second only to water in popularity as a beverage. The antioxidant components in tea leaves include methylxanthines and polyphenols, especially flavonols of the catechin type: (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin and (Lambert 2002).

In Table 1 are presented selected studies that show the potential chemopreventive effects of EGCG.

However, their therapeutic potential is limited by their low oral bioavailability, attributed to poor stability and intestinal absorption. Whereas green tea catechins are very unstable in neutral and alkaline solutions they are relatively stable under acidic conditions. It was found that EGCG degraded faster with the increase of either pH, oxygen concentration or temperature (Zimeri and Tong ,1999). EGCG was found to be unstable in simulated intestinal fluid pH 7.4, conditions under which 80% of it was lost in only 1h (Dube 2010).

Table 1 - Studies made to demonstrate chemopreventive effects of EGCG.

Chemopreventive effect	*in vitro in vivo*	Reference
Stimulation of detoxification systems: selective induction or modification of phase I and phase II metabolic enzymes which increase the formation and excretion of detoxified metabolites of carcinogens;	*in vitro*	Weisburger *et al*, 1999
Anti-inflammatory, antimutagenic, anti-angiogenic, antiproliferative;	*in vitro in vivo*	Clair *et al.*, 2002
Initiation, promotion and progression in animal models of oral, lung, duodenal, prostate, liver and colon cancers;	*in vivo*	Lambert *et al.,* 2004
Inhibition of colorectal crypt foci formation in azoxymethane-treated F344 rats;	*in vivo*	Xiao *et al,* 2008
Inhibits: VEGF/VEGFR axis, activation of several other RTKs, including IGF-1R, EGFR, HER2, and HER3 in colon cancer cells (suppressing expression of HIF-1 and growth factors)	*in vitro in vivo*	Shimizu *et al.,*2010

Micro or nanoparticle (MP/NP) mediated delivery of phytochemicals can serve a basis for enhancing bioavability, better encapsulation, control release and limiting the unwanted toxicity properties of chemopreventive agents (Singh 2011). The MP/NP drug delivery systems offer numerous advantages over the conventional dosage forms: improved efficacy, reduced toxicity, and increased stability (Coppi 2002). We consulted bibliographic references from international journals and official documents from recent years related with the encapsulation of ECGC.

O/W emulsions stabilized by ι-carrageenan and β-lactoglobulin. EGCG can be successfully encapsulated by this mean when its concentration is <0.5%. If concentration is >0.5%, significant instability of the O/W emulsions due to the binding between EGCG and β-lactoglobulin is observed. EGCG in an O/W submicrometer emulsion reveals an enhanced *in vitro* anticancer activity compared to the free EGCG (Qiaomei 2010).

Gum arabic-maltodextrin NPs. NPs loaded with EGCG by homogenization and spray drying technique, with an EGCG loading efficiency of 96±3%. EGCG was incorporated in the carbohydrate matrix by intermolecular interactions, maintaining its chemical integrity (Peres 2011).

Eudragit® S100 microspheres. EGCG-loaded microspheres (EGCG/MS), contained Eudragit® S100, with an emulsion solvent diffusion method in aqueous polyvinyl alcohol solution. The EGCG/MS exhibited pH-dependent controlled release of EGCG with limited initial burst release, and the Eudragit® S100-based MS also had moderate bioadhesive property in isolated small intestine of rats. Significant improvement in chemical and metabolic stability of EGCG was observed, possibly due to the controlled release and/or bioadhesion (Satomi 2011).

Liposomes. Liposomes (LP) containing EGCG were injected into basal cell carcinomas, melanomas, and colon tumors. Almost no drug molecules were observed when free EGCG was administered. EGCG encapsulated in LP with deoxycholic acid and ethanol increased drug deposition compared to the free form. The LP without ethanol showed low or negligible enhancement on EGCG uptake. LP induced of greater apoptosis compared to that by free EGCG at lower concentrations (Fang 2006).

Pectin beads. Lee *et al* (2009) studied calcium pectinate gel (CPG) beads entrapped catechin-loaded LP prepared with or without hydroxypropylmethylcellulose (HPMC) and characterized in comparison with the CPG beads prepared without LP and HPMC. The catechin release was slowed by LP and further retarded when HPMC was used simultaneously, whereas not in simulated gastric fluid. Antioxidant activity of catechin in rat plasma was more effectively maintained when the catechin-loaded MP were fed.

Chitosan NPs. Dube *et al.* (2010) showed that EGCC in CS NPs significantly enhances their *in vitro* intestinal absorption, which most likely occurs as a result of the stabilization of catechins in the donor chamber, which subsequently drives their flux across the tissue.

CONCLUSION

The use of EGCG can prevent colorectal cancer, and may also be a tool to use concomitantly with oral chemotherapy treatments. Pectin is suitable for use as colon-specific drug delivery vehicle as it is selectively digested by colonic microflora to release drug with minimal degradation in upper gastrointestinal tract. The most used compound is CS, due to its profuse adherence to intestine mucosa: it possesses absorption enhancing properties, and can increase the ability of drugs to permeate through the paracellular route through a reversible opening of epithelial tight junctions.

MP/NPs drug delivery systems for EGCG offer numerous advantages. Further investigation is required in order to improve the preventive and therapeutic effects through a multi-disciplinary approach.

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