International Journal of Pharmaceutics 518 (2017) 220–227

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

# Cancer therapeutics with epigallocatechin-3-gallate encapsulated in biopolymeric nanoparticles

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ARTICLE INFO

*Article history:*
Received 17 August 2016
Received in revised form 28 November 2016
Accepted 12 December 2016
Available online 14 December 2016

*Keywords:*
Cancer
Green tea
EGCG
Biopolymers
Nanoparticles

ABSTRACT

With the recent quantum leap in chemoprevention by dietary products, their use as cancer therapeutics is garnering worldwide attention. The concept of effortlessly fighting this deadly disease by gulping cups of green tea or swallowing green tea extract capsules is appreciated universally. Epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea, has generated significant interest in controlling carcinogenesis due to its growth-inhibitory efficacy against a variety of cancers by targeting multiple signaling pathways. However, the success of EGCG in preclinical studies is difficult to translate into clinical trials due to issues of low solubility, bioavailability and an uncertain therapeutic window. The laborious and expensive journey of drugs from the laboratory to commercialization can be improved by utilizing nanoparticles as anti-cancer drug carriers. Exploitation of biopolymeric nanoparticles in recent years has improved EGCG's biodistribution, stability and tumor selectivity, revealing its superior chemopreventive effects. This review briefly summarizes recent developments regarding the targets and side effects of EGCG, complications associated with its low bioavailability and critically analyses the application of biopolymeric nanoparticles encapsulating EGCG as a next generation delivery systems.


**Contents**



## 1. Introduction

Cancer remains a major challenge owing to the diversity of affected patients, the multitude of sites involved, and the poor efficacy of many conventional treatments. The complexities of targeting cancer at the genetic and phenotypic levels represent a challenging task (Penny and Wallace, 2015). Among the numerous treatment strategies employed, the use of nutraceuticals such as plant polyphenols and carotenoids holds chemopreventive potential against diverse cancer types (Yang et al., 2002). Recent evidence demonstrates that polyphenols such as Curcumin, Resveratrol, Quercetin, etc. found in fruits, vegetables and other plant parts possess cancer-preventive effects and can inhibit growth of cancer cells (Aras et al., 2014; Summerlin et al., 2015; Popat et al., 2014). Similarly, in the past few years the anti-cancer potential of "green miraculous drink" *i.e.* green tea and its

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http://dx.doi.org/10.1016/j.ijpharm.2016.12.030
0378-5173/

catechins, have been demonstrated in animal models involving multiple cancer types. The probable mechanisms identified that hamper cancer development and/or progression include inhibition of proliferation, initiation of apoptosis, and suppression of critical processes including invasion, migration and angiogenesis (Ju et al., 2007). Therefore, there is the potential to reap the benefits of a pleasantly flavoured medicinal drink with multiple health benefits against a myriad of illnesses, including cancer (Higdon and Frei, 2003).

Next to water, tea is the major consumed beverage worldwide, prepared from the dried leaves of *camellia sinensis* (Yang and Wang, 2010). Alternative forms of tea can be obtained by different preparation techniques, including the major varieties of green, black and oolong tea. Green tea contains polyphenols commonly known as tea catechins, such as (−)Epigallocatechin-3-gallate [EGCG], (−)Epigallocatechin[EGC], (−)Epicatechin-3-gallate[ECG] and (−)Epicatechin[EC] which account for their major biological and pharmacological activities (Yang et al., 2009). Catechins present in green tea constitute 33% of the total dry weight, which is significantly higher than red and oolong tea (Wang et al., 2006). Among the catechins, EGCG is of high importance due to its abundance, constituting 50–80% of total catechin content in green tea, which is equivalent to 200–300 mg/brewed cup. In addition its safety profile, easy availability and simple extraction procedure set it apart from other polyphenols (Khan et al., 2006). EGCG possesses several therapeutic properties including anti-oxidant, anti-proliferative, anti-angiogenic and anti-carcinogenic effects (Singh et al., 2011). EGCG is an example of a class of monomeric flavan-3-ols which are characterized by hydroxylated aromatic rings. The presence of a pyrogallol-type structure and gallolyl moiety on separate rings of EGCG are strongly associated with induction of apoptosis, formation of reactive oxygen species and cytotoxic activities against cancer cells (Saeki et al., 2000; Du et al., 2012; Braicu et al., 2011). A plethora of epidemiological, cell-based studies, animal models and clinical trials have provided convincing data to support EGCG's anti-cancer effects. EGCG modulates multiple cancer-related pathways, including downregulation of redox-sensitive transcription factors (eg NFκB), triggering of programmed cell death through upregulation of Bcl-2, inhibition of angiogenic molecules incldiung VEGF, induction of cell cycle arrest at GO/G1 phase, and modulation of intracellular signal transduction pathways such as MAPK and PI3 K/AKT (Kim et al., 2014).

Adding to the benefits of EGCG, newer data gleaned from pharmacokinetic studies suggest that after green tea intake a majority of the plasma population (>75%) represents free EGCG rather than EGC and EC (Meng et al., 2002; Kotani et al., 2003; Umegaki et al., 2001). Interestingly no detectable amounts of EGCG or its metabolite 4′,4′-DiMeEGCG have been detected in urine samples, despite significant plasma concentrations, suggesting a non-renal mediated clearance (Clifford et al., 2013). Excretion of EGCG in rats occurs *via* the hepatic route, which is the presumed route in humans as well (Kohri et al., 2001). This may explain the longer elimination half-life of EGCG in the body ($3.4 \pm 0.3$ h) compared to other catechins (Lee et al., 2002). Despite low systemic circulation, EGCG was still found in human prostate tissue (Wang et al., 2010) animal tissues of mice (Kim et al., 2000), foetuses, placenta (Chu et al., 2006), and the brain of rats (Lin et al., 2007) suggesting distribution properties that could be exploited for other medical conditions. Clearly EGCG possess great potential in cancer treatment and prevention but low bioavailability, inappropriate systemic release and bioaccessibility has limited the role EGCG in clinical settings. Although there are several aspects of EGCG biology, pharmacodynamics, and pharmacokinetics to be better understood in order to target cancer effectively (Fig. 1), improving the bioavailability and site specific delivery are presumed to be fundamental to enhancing its efficacy.

Oral bioavailability of EGCG is less than 2% of the administered dose in rats (Chen et al., 1997) and below 20% in mice (Lambert et al., 2003). The interpretation of EGCG bioavailability in humans is hampered by a lack of adequate information as most studies examined the pharmacokinetics of tea catechins. Oral bioavailability of EGCG is affected by several factors such as molecular weight, pH, biometabolic conversions, presence of metal ions, temperature and oxygen concentration (Mereles and Hunstein, 2011).

High molecular weight catechins, a greater number of hydroxyl groups and presence of a gallolyl moiety in EGCG accounts for its inability to pass through the intestinal epithelium resulting in poor bioavailability (Warden et al., 2001). Degradation of EGCG increases with relative humidity and temperature, as demonstrated using spray dried green tea extract, thus lowering its

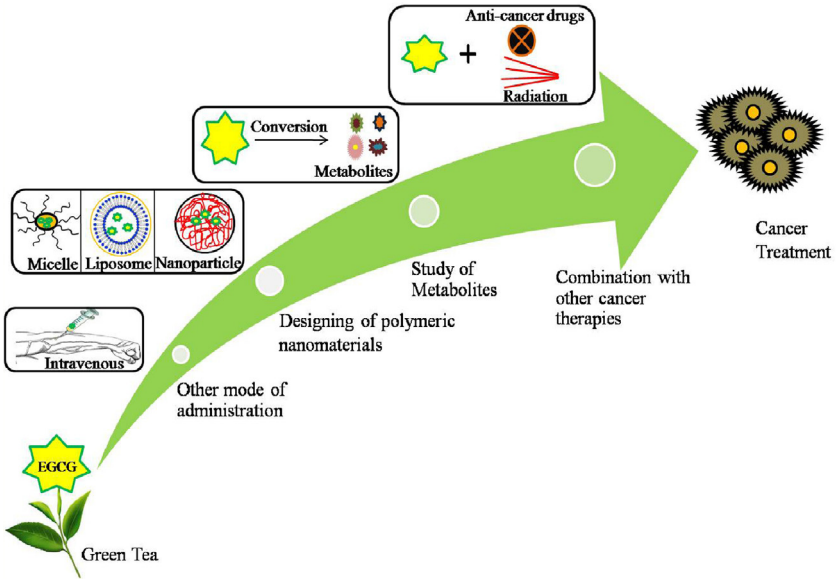


**Fig. 1.** Major areas requiring investigation for exploiting the anti-cancer potential of EGCG using drug delivery.