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EGCg-AuNPs Nanotherapeutics – as an alternative Green Nanotechnology approach for treating cardiovascular diseases

Cardiovascular diseases are the leading cause of morbidity and mortality in the United States and globally. However, despite remarkable technological advances, significant limitations remain in stent-based treatment. Therefore, it is important to develop selective and effective therapeutics with minimal or no adverse effects to patients. In our ongoing research on the application of nanotechnology to medicine, we have developed a library of functionalized hybrid gold nanoparticles using Green Nanotechnology approaches. In this approach, we have demonstrated that naturally occurring antioxidant-phytochemicals can be used as electron injectors to produce biocompatible gold nanoparticles without the intervention of any toxic chemical. We have also shown that nanoencapsulation of phytochemicals-based formulations are effective in enhancing drug efficacy, increasing drug tolerance, and in improving targeted drug delivery. Gold nanoparticles, produced through our Green Nanotechnology approaches, offer tremendous opportunities for the development of next generation of nanoceuticals. In this report, we discuss the utility of epigallocatechin gallate (EGCg), a phytochemical from tea leaves, for the production gold nanoparticles (EGCg-AuNPs). Such gold nanoparticles are encapsulated with EGCg rendering them inherent affinity to laminin receptors which are overexpressed on smooth muscle cells (SMCs). Overall, this innovative approach eliminates the use of toxic chemicals for the production of therapeutic nanoparticles for use in various pharmaceutical applications.

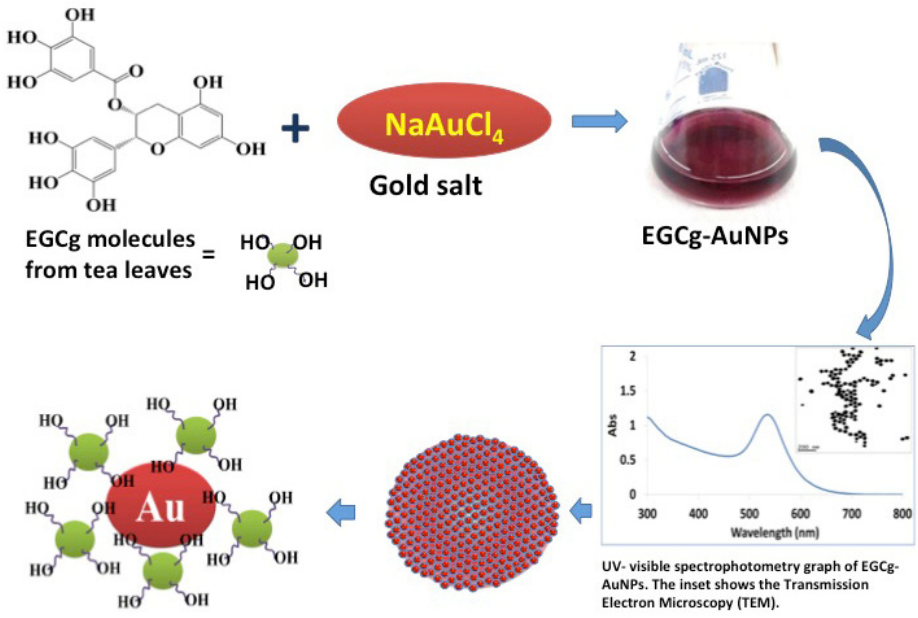
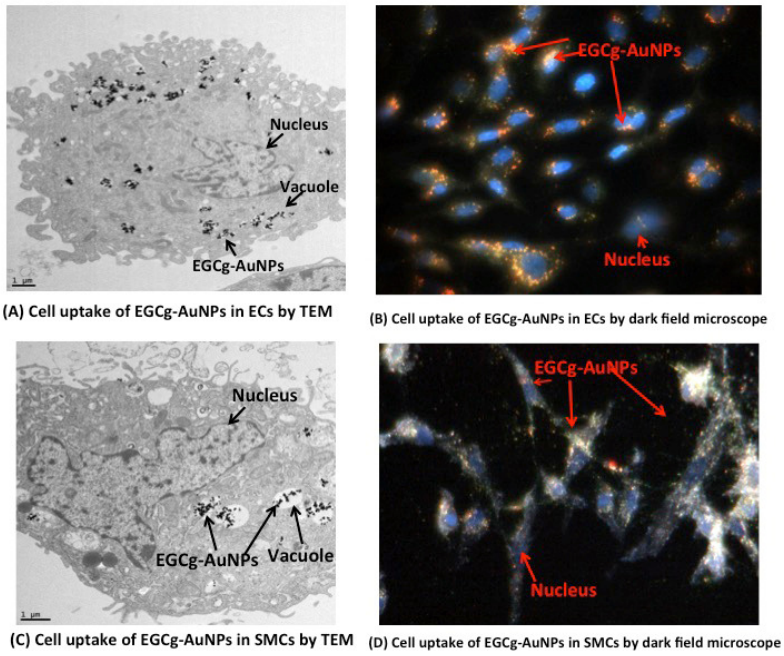


Fig. 1. EGCg molecules conjugated gold nanoparticles (EGCg-AuNPs).

Numerous studies have described that the stent placement leads to post-treatment adverse effects in patients. Major life threating complications with stent placement include stent thrombosis (blood clot formation) and in-stent restenosis, resulting in high rates of death and nonfatal myocardial infraction (heart

attack). However, drug-coated stents are an alternative to inhibit the proliferation in the vascular wall but they inhibit the regrowth of endothelial cells. Delayed endothelial-healing renders the artery vulnerable to blood clot formation, which can abruptly obstruct blood flow and cause heart attack. Epidemiologic studies have demonstrated an association between intake of antioxidant (phytochemicals-polyphenols) with decreased risk for dreadful cardiovascular and cancer related diseases. We, herein, report on the development of EGCg-AuNPs as selective and effective vehicles for the delivery of EGCg as a safe clinical modality for treating cardiovascular diseases.

EGCg-AuNPs were prepared by simple mixing of gold salt with EGCg solution at room temperature in aqueous media (Figure 1). This procedure does not involve any toxic chemicals and that EGCg-AuNPs have a long shelf life (2 years or more). One key objective of our research was to improve the bioavailability and efficacy of EGCg by encapsulating onto gold nanoparticles. With this approach, we have achieved significant efficacy and selectivity of EGCg towards the smooth muscles cells (SMCs) and endothelial cells (ECs), which line the inner surface of the vessels. The results obtained in our investigations suggested that EGCg-AuNPs internalized in cells through laminin receptor mediated endocytosis within a short time (Figure 2). The cytotoxicity profile of EGCg-AuNPs towards both SMC and EC cell lines was tested. We observed that EGCg-AuNPs inhibited the migration of SMCs, without affecting the growth of endothelial cells. It is important to note that SMCs cause the plaque formation inside the blood vessels and therefore it is essential to control the growth of SMCs without destroying the ECs. The results reported in the published paper have confirmed the selective affinity of EGCg-AuNPs towards the SMCs. With this approach, we have validated our hypothesis that conjugation of EGCg onto gold nanoparticles enhances their bioavailability and selective delivery of EGCg.



(A) Cell uptake of EGCg-AuNPs in ECs by TEM

(B) Cell uptake of EGCg-AuNPs in ECs by dark field microscope

(C) Cell uptake of EGCg-AuNPs in SMCs by TEM

(D) Cell uptake of EGCg-AuNPs in SMCs by dark field microscope

Fig. 2. Cell uptake of EGCg-AuNPs in endothelial (A-B) and smooth muscles (C-D) cells.

Our proprietary technology would therefore allow immobilization of high doses of EGCg onto biocompatible gold nanoparticles thus opening up realistic applications in treating and preventing various cardiovascular conditions including restenosis after stenting. This innovative nanomedicine intervention brings about a paradigm shift as an alternative to drug coated stents for the effective treatment of coronary bifurcation lesions including prevention of vascular wall thickening and thrombosis.

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Publication

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