REVIEW ARTICLE

An Insight of Epigallocatechin-3-gallate-loaded Gold Nanoparticles as an Oral Mucosal Cancer Adjuvant Therapy by Modulating Intrinsic Apoptosis Pathway: A Narrative Review

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ABSTRACT

Oral mucosal cancer is a type of cancer with high recurrence. Tobacco smoking, alcohol, and virus are the main etiology. During the centuries, treatment options for this cancer are surgery, chemotherapy, and radiotherapy despite being considered as invasive treatments, high cytotoxicity to normal tissue, and potential for metastasis. Epigallocatechin-3-gallate (EGCG) is a non-toxic biomaterial that induces intrinsic apoptotic cascade, but oral administration results in low bioavailability thus combining with gold nanoparticles (GNPs) as drug carriers. EGCG-loaded GNPs interact with laminin receptors then endocytosed and encapsulated. EGCG-loaded GNPs combined with photothermal therapy convert light into oscillating electrons and change GNPs into charged material that potentially induces double-strand breaks leading to p53 activation. Activation of p53 modulates the expression of various pro-apoptosis proteins thus leading to apoptosome formation to activate caspase-3, which manifests in the formation of apoptotic bodies.

Keywords: apoptosis, epigallocatechin-3-gallate, gold nanoparticles, oral cancer

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INTRODUCTION

Cancer is defined as an abnormal growth of cells and becomes the leading cause of death worldwide [1, 2]. Oral mucosal cancer is the biggest cancer predilected in the oral cavity with various etiological factors including alcohol, tobacco smoking, and virus [3]. During the centuries, treatment options for this cancer are varying from surgery, radiotherapy, and chemotherapy despite being considered as invasive treatments, high cytotoxicity to normal tissue, and potential to metastasis thus lowering the prognosis of disease [4–7]. Green tea (*Camellia sinensis L.*) is a plant that is commonly used in cancer therapy by the content of its major polyphenol named epigallocatechin-3-gallate [8–10]. Epigallocatechin-3-gallate or EGCG has shown its ability to induce apoptosis and hinder metastasis, angiogenesis, and proliferation of skin melanoma and colorectal adenoma cell [11, 12]. Nevertheless, oral administration of EGCG decreases its bioavailability by enzymatic degradation provided by gastrointestinal tract thus lowering its therapeutic effect [13, 14]. Gold nanoparticles (GNPs) are drug carriers with the diameter ranging from 50-150 nm and supported by high bioavailability and functionality [15, 16]. In cancer therapy, GNPs are often combined with photothermal therapy, a therapy utilizing light exposure with a certain wavelength accompanied by the mechanical properties of GNPs as a photo-absorbing agent that can induce light conversion into heat leading to protein destruction [17–19]. Combination of EGCG and GNPs is able to penetrate to the cell by interacting with laminin receptors leading to endocytosis. EGCG-loaded GNPs increase the permeability of the outer mitochondrial membrane thus leading to the subsequent release of apoptosome-forming proteins so that the formation of apoptosome is increased. The presence of apoptosome activates caspase-3, a major inisiator of intrinsic apoptosis pathway, resulting in the formation of apoptotic bodies [17, 20–22]. Therefore, this narrative review is conducted in order to determine the role of EGCG-loaded GNPs in modulating intrinsic apoptosis pathway in oral mucosal cancer.

REVIEW

Oral Mucosal Cancer

Pathogenesis of oral mucosal cancer is started by

exposure of carcinogenic agents such as tobacco smoking and alcohol. This condition leads to an increase in inflammatory cell migration manifests in the overproduction of oxidants such as reactive oxygen species (ROS) and nitrogen oxide species (NOS) that are able to induce destruction and breakdown of DNA of keratinocytes. This condition activates proto-oncogene and epithelial growth factor receptor (EGFR) thus activating Rat sarcoma-signal transducer and activator of transcription 3 (RAS-STAT3) and MYC as the marker of initiation stage. This stage is able to induce hypoxia that upregulates ROS content in the mitochondria. Continuous repeats of this condition leading to a wider deoxyribonucleic acid (DNA) breakdown thus promoting the development of initiation stage into the promotion and progression stage of oral mucosal cancer [23, 24].

Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate or EGCG is the major polyphenol compound of green tea (Camellia sinensis L.) with a percentage of 32,77%-75,05% [25]. EGCG is widely used in cancer therapy by its ability to upregulate the expression of p53. As consequence, protein kinase B (Akt) expression is lowered while p53 upregulated modulator of apoptosis (Puma) and Noxa are upregulated thus leading to the decrease of anti-apoptosis protein [26, 27]. This condition induces Bcl2-associated X protein (Bax) translocation into the outer mitochondrial membrane thus leading to the opening of mitochondrial pores [28–32]. This condition leads to the subsequent release of cytochrome c then interacts with apoptotic protease activating factor-1 (Apaf-1), pro-caspase-9, and adenosine triphosphate (ATP) to form an apoptosome in order to activate caspase-3 and enhance the formation of apoptotic body [33–35].

Gold Nanoparticles

Gold nanoparticles (GNPs) are gold-based drug carriers with a diameter ranging from 50-150 nm [36]. GNPs have some properties including high bioavailability, stability, and functionality [18, 37]. Application of GNPs in cancer therapy is mediated by its important role as photo-absorbing agent in combination with photothermal therapy. Absorbed light is converted into heat with surface plasmon resonance (SPR) ability of GNPs then facilitates light conversion into oscillating electrons that produce heat. GNPs are able to penetrate into the cancer cell and convert the light into heat ranging from 42-45°C leads to the increase of susceptibility of the cell under pharmacological treatment and destruction of organelles [38–41].

Intrinsic Apoptosis

Intrinsic apoptosis is one of the major pathways of apoptosis which is specifically mediated by Bcl-2 family and caspase, a part of protease that is formed by cysteine-aspartyl complex and acts as an enzyme precursor [42, 43]. Induction of intrinsic apoptosis is the consequence of p53 expression leads to the decrease of anti-apoptotic protein expression and upregulation of pro-apoptotic protein. This condition is able to induce the opening of mitochondrial pore thus promoting cytochrome c release as an apoptosome-forming protein and second mitochondria-derived activator of caspase/direct inhibitor of apoptosis (IAP)-binding protein with low pI (SMAC/Diablo). They prevent the fixation of certain subdomains of X-linked inhibitor of apoptosis protein (XIAP) that is able to disrupt the activation of caspase 3/9 [33, 34, 44, 45] Apoptosome activates caspase-3 thus inducing membrane blebbing and retraction of the cell manifests in the formation of apoptotic bodies then phagocytosed by macrophage [46, 47].

DISCUSSION

EGCG-loaded GNPs are injected into the body and reach the target cell by infiltrating the blood vessel. This condition is facilitated by impaired angiogenesis in cancer which is resulted in the formation of blood vessels with broad interstitial distance within each endothelial cell, which then facilitates GNPs to intravasate by exiting the vessels and entering the cancer cell [48–50]. EGCG can interact with laminin receptors thus promoting endocytosis of GNPs [17].

Previous research showed that EGCG-loaded GNPs in the concentration of 48% and 34,7% enhance apoptosis prostate cancer 3 (PC3) and M.D Anderson - Metastatic Breast 231 (MDA-MB-231) cell lines [17]. EGCG acts synergistically with GNPs in inducing apoptosis. The use of GNPs as drug carriers is also supported by their ability to induce apoptosis by two different mechanisms, mainly by inducing pro-apoptosis protein expression through heat generation and enhancing double-strand breaks (DSB) formation by electron accumulation. Utilization of GNPs for this condition is started by combining with near-infrared (NIR) light, a light with a wavelength ranging from 600-1000 nm that is applicable in the form of photothermal therapy (PTT). GNPs have electrons that occur on the surface thus making this material hold electric force. Light is recognized as electromagnetic waves. When GNPs are irradiated into electromagnetic waves, the interaction between the electrical force of GNPs and electromagnetic force resulted in light diffraction and excitation of electrons held by GNPs with certain angles as induced by photons of light, then disseminated parallelly to the GNPs' surface. Subsequently, electrons in the surface of GNPs oscillate and then resonate with oscillation of electric force by NIR light resulting in the generation of plasmonic energy thus producing heat, whereas this phenomenon is well-recognized as surface plasmon resonance (SPR), a special term in metal-based material especially GNPs [51–53]. The heat produced by GNPs is sufficient to modulate the expression of certain proteins as it increases intracellular temperature by about 17°C, maximally [37]. This condition then induces Noxa and

Puma expression as pro-apoptosis proteins, as well as downregulating several anti-apoptosis proteins including B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-XL) and myeloid-cell leukemia 1 (MCL-1) [44, 45]. Oscillating plasmons on the surface of GNPs turned this material into charged material that needed to be conjugate to other molecules turning them into a stable conformation, as this principle is totally similar with oxidants. This condition increases susceptibility to promote binding into certain molecules although it means that GNPs possibly break and re-conformate the structure of proteins or molecular substances within the cell. This facilitates GNPs to bind into genetic material located in the nucleus and stick to them then manifests in cross-linking and breaks of DNA [54, 55]. Both conditions are often recognized as genotoxic stress, thus activating ataxia telangiectasia and Rad3-related (ATR-Chk2) then stabilizes and induces the phosphorylation of p53 in cancer cells. For example, p53 gene is known to increase in post-exposure of x-ray in GNPs after 6 and 24 hours thus manifested in the activation of apoptosis cascade [56, 57].

The ability of GNPs to upregulate p53 expression and produce heat is supported by the ability of EGCG itself to induce Sirtuin 1 and inhibit signal transducer and activator of transcription 3 (STAT3) and murine double minute 2 (MDM2) expression resulting in p53 translocation into the nucleus [26, 58, 59]. These conditions are able to downregulate the expression of Akt. Akt or protein kinase B is an oncogene protein that regulates apoptosis, proliferation, and survival of the cell [60]. Downregulation of Akt is accompanied by the increase of Puma and Noxa thus suppressing the expression of Bcl-2, Bcl-xL, and Mcl-1 as anti-apoptotic proteins [42, 44, 61]. This condition leads to the increase of Bcl-2-like protein 11 (Bim) that facilitates conformational changes of Bcl-2 homologous antagonist killer (Bak) resulting in Bak activation [62]. This condition is accompanied by an increase of BID induce caspase-8 expression so that BID cleaved into truncated BID (tBID) and then interacts with Bcl-2 homologous antagonist/killer (Bak). Formation of tBID-Bak complex triggers Bak oligomerization then induces Bax translocation from cytosol to the outer mitochondrial membrane. Translocation of Bax results in the formation of heteromers thus lowering mitochondrial membrane potential ($\Delta\Psi m$) then mitochondrial pores are opened [29, 31, 32]. On the other hand, the opening of mitochondrial pores is also caused by EGCG's ability to induce excess uptake of $Ca2+$ in mitochondria by activating voltage-dependent anion channels (VDACs) located in the outer mitochondrial membrane and mitochondrial calcium uniporter (MCU) originating the inner mitochondrial membrane induces the increase of $Ca2+$ influx from endoplasmic reticulum, resulting in an increase of $Ca2+$ of mitochondria. At this condition, $Ca2+$ interacts with cyclophilin D to induce the opening of mitochondrial pores [20, 63].

The opening of mitochondrial pore manifests in a subsequent release of cytochrome c, Htr2/Omi, and SMAC/Diablo from mitochondrial membrane into cytosol. This condition is supported by the E2 factor (E2F) induces Apaf-1 synthesis so that Apaf-1 expression in cytosol is increased and activated by the fixation of ATP. Apaf-1 oligomerizes with cytochrome c by interacting in the caspase recruitment domain of Apaf-1 then bind together with pro-caspase-9 and ATP to form a heterodimer structure called an apoptosome. Apoptosome induces proteolytic activity thus resulting in the formation of active site caspase-3 [33–35].

On the other hand, Smac/Diablo and Htr2/Omi that are previously released together with cytochrome c play an important role in preventing caspase-3/9 suppression from the XIAP family. XIAP or X-linked inhibitor of apoptosis protein is a protein acting as a caspase inhibitor by binding its subdomains into caspases. The SMAC/Diabloand Htr2/Omi are able to bind tand degrade XIAP thus their certain subdomains such as BAK2-interacting receptor-like kinase (BAK2) are not able to bind to caspase-3, neither does BAK3-interacting receptor-like kinase (BAK3) to caspase-9 thus resulting in activation of caspase-3/9 [64–66].

Activation of caspase-3 increases the hydrostatic pressure of the cell accompanied by cell contraction by actomyosin resulting in membrane blebbing. This condition is repeated and then manifests in cell retraction. At this condition, caspase-3 induces caspase-activated DNase endonuclease so chromosomes of DNA are degraded and manifests in chromatin condensation, nucleus fragmentation, and shrinkage of the nucleus accompanied by destruction of cell's membrane, resulting in the formation of apoptotic bodies covered by cell organelles and genetic substances [67, 68]. Apoptotic bodies contain high phosphatidylserine levels making them discoverable by immune cells and then phagocytized by macrophages [46, 47].

CONCLUSION

According to the review, EGCG-loaded GNPs have potential as an oral mucosal cancer adjuvant therapy by their synergism to undergo intrinsic apoptosis through multiple different mechanisms. Further research should be conducted in order to prove and evaluate the possibility of this combination as a promosing drug candidate in the future.

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