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Integrative Medicine Research

journal homepage: www.imr-journal.com

Review Article

Chemopreventive role of green tea in head and neck cancers

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ARTICLE INFO

Article history:
Received 10 November 2013
Received in revised form
6 December 2013
Accepted 10 December 2013
Available online 17 December 2013

Keywords:
chemoprevention
green tea
head and neck cancer

ABSTRACT

In the era of personalized medicine, selecting the ideal treatment modality for head and neck cancer is becoming more complex. Also, despite the use of the newest agents, overall survival has not been improved notably over the past few decades. Currently, in accordance with the development of diagnostic tools, prevention and early detection of cancer are being emphasized more in obtaining better treatment outcomes. Among the various cancer preventative methods, the use of green tea is one of the most common approaches, and tea is known to be involved in multiple steps of carcinogenesis. Thus, in this short review, the protective roles of green tea components against the initiation, progression, and metastasis of head and neck malignancies will be discussed.

1. Introduction

Green tea, produced from the plant *Camellia sinensis*, is one of the most popular beverages in East Asian countries. Recently, due to multiple positive effects on various health conditions, the popularity of green tea has increased further. The components of green tea include proteins, carbohydrates, lipids, vitamins, caffeine, theophylline, carotenoids, and polyphenols. Among these, polyphenols are the most interesting constituent and have become the focus of much biomedical research.

The major polyphenols in green tea are catechins. The major catechins are epigallatocatechin-3-gallate (EGCG), (–)-epicatechin-3-gallate (ECG), (-)-epigallatocatechin (EGC), and (–)-epicatechin. Among these, EGCG is the key catechin, accounting for up to 80% of the total catechins; a cup of green tea contains ~300 mg.

A previous work has demonstrated diverse beneficial effects of EGCG in Parkinson's disease, Alzheimer's disease, diabetes, stroke, and even obesity.[1] In addition to these beneficial properties of EGCG, effects related to cancer prevention and treatment have been reported.

Because prevention and early detection improve the treatment outcome in every known cancer type, the concept of "chemoprevention" is becoming more significant in cancer research. Chemoprevention can be defined as the use of natural or synthetic substances to prevent or suppress the development, progression, and metastasis of cancer. A representative natural product used for chemoprevention of cancer is EGCG, which has been demonstrated to exert various positive effects on colon, breast, stomach, esophagus, lung, and prostate cancers and on melanoma.

Head and neck carcinoma, including thyroid cancer, is a common cancer that remains a significant cause of mortality

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http://dx.doi.org/10.1016/j.imr.2013.12.005

and devastating morbidity. In the United States, over 48,000 new cases of this carcinoma are diagnosed annually, of whom more than 10,000 die. Most cases of head and neck cancer are treated by surgical intervention initially. Owing to the complexity of the anatomical structures in the head and neck area, complete and wide surgical extirpation of the disease can result in severe morbidity, in both functional and esthetical respects. Although medical and radiation therapies have been used widely to overcome and compensate for the weak points and morbidities related to surgery, these conventional treatment modalities have not improved the overall survival rate.

Thus, in accordance with the development of diagnostic technologies, early detection and prevention of carcinogenesis have been emphasized to improve the treatment outcome. That is, new approaches to cancer management, such as chemoprevention, should be considered and used to alter the overall survival rate. Several clinical applications and trials using natural products such as chemopreventive agents have demonstrated successful outcomes in terms of preventing cancer development in high-risk individuals. Here, we review recent research works on the effects of green tea and discuss future directions in head and neck cancer prevention.

2. Head and neck squamous cell carcinoma

Among the various cancers of the head and neck, squamous cell carcinoma (SCC) is the most common. As SCC development in this region is associated with different clinical courses and treatment outcomes according to the primary site, research outcomes regarding each site should be considered separately. In terms of the mechanisms of action of green tea components in head and neck SCC, induction of apoptosis and growth arrest and inhibition of metastasis are the two main research foci.

2.1. *Oral cavity and pharyngeal cancer*

Inducing the apoptotic process is a highly programmed protective mechanism that eliminates damaged cells from the body. Regarding carcinogenesis, cancer cells, which grow excessively regardless of homeostasis, should be eliminated by apoptosis. Thus, many previous studies have focused on enhancing apoptosis by treatment of the oral cavity cancer and pharyngeal SCC cell lines with green tea components.

The major catechin of green tea, EGCG, has been used in previous studies related to apoptosis induction.

The simplest work involves evaluation of cell viability and DNA synthesis levels in green-tea-component-treated oral squamous cancer cells (SCC-25).[2] Dose-dependent and direct cytotoxic effects of EGCG, ECG, and EGC have been shown. Inhibition of DNA replication was also detected after the treatment.

A cytotoxic effect of EGC in the human squamous cancer-2 cell line has been reported. The focus was on the intracellular reactive oxygen species, hydrogen peroxide, generation of which increased after EGC treatment compared with the levels in normal cells. This increased level of hydrogen peroxide caused degradation of nucleosomal DNA and induced caspase-3 activity, which accelerated cell death.[3,4]

With the exception of these two studies that focused on direct cytotoxic effects of green tea components, other research works on the relationship between green tea and oral cavity/pharyngeal SCC have focused on the modulation of cell signaling by green tea. Although cytotoxic effects of EGCG, EGC, and ECG have been reported, only EGCG has been found to exhibit signaling modulation activity.

Among signaling molecules, cyclin-dependent kinase and related molecules are the primary targets for EGCG. Expression of an apoptosis inhibitor and a cyclin-dependent kinase, p57, were elevated in normal keratinocytes in dose- and time-dependent manners, whereas the levels in the SCC25 and OSC2 oral carcinoma cell lines were consistent.[5] This expression pattern was correlated with the apoptosis status of treated cells, confirming the chemopreventive effect of EGCG. Although this report mentioned modulation of apoptosis by p57, the whole apoptotic cascade was not considered. Another molecule, p21WAF, which plays a role in cell growth, differentiation, and apoptosis, was upregulated in the oral carcinoma cell line, OSC2, after treatment with EGCG. Using a p21WAF siRNA, the EGCG-induced overexpression of this molecule was shown to enhance caspase 3-mediated apoptosis.[6]

Epidermal growth factor receptor (EGFR) is a plasma membrane protein that has an intrinsic tyrosine kinase activity. A cancer cell phenotype is known to result from the overexpression of this receptor. As in colon cancer cells, SCC of the head and neck frequently exhibits upregulation of EGFR expression.[7,8] EGCC treatment of SCC cells first results in the inhibition of EGFR phosphorylation. Afterward, downstream proteins, such as signal transducer and activator of transcription 3 (Stat3), and extracellular regulated kinase (ERK), are inhibited sequentially. Other proteins, such as basal and transforming growth factor-α-stimulated c-fos and cyclin D1, were also downregulated, with the consequent significant arrest of cell growth and proliferation.[8] Similarly, HER-2/neu receptor (HER-2), known to be associated with a poor prognosis in patients with breast carcinoma, was modulated by EGCG in head and neck SCC.[9] The working mechanism of action of EGCG against HER-2 was identical to that against EGFR. Accordingly, downstream proteins, such as Stat3, c-fos, cyclin D1, and Bcl-XL were inhibited in order. We also presented a novel target for chemoprevention using EGCG in head and neck SCC. Nonsteroidal anti-inflammatory drug-activated gene-1 (NAG-1) is a member of the transforming growth factor-β superfamily, known to be involved in inflammation, apoptosis, and carcinogenesis.[10] As the role and mechanism of NAG-1 in carcinogenesis are controversial, according to the primary site of the cancers, we focused on determining the role of this protein in SCC of the head and neck.[11–13] EGCG induced NAG-1 expression at the transcriptional level, which was directly related to EGCG-induced apoptosis in the KB cell line through caspase-3 activation. We also demonstrated that ataxia telangiectasia-mutated protein functions to activate NAG-1, p53, and p21, consequently facilitating apoptosis. Another strong point of our work was the *in vivo* result obtained using an immunocompetent syngeneic mouse model and intraperitoneal EGCG injection. The results being identical to those *in vitro* provided evidence for not only a new mechanism of head and neck SCC development, but also a promising target for new therapeutic agents.