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Chemopreventive and therapeutic modulation of green tea polyphenols on drug metabolizing enzymes in 4-Nitroquinoline 1-oxide induced oral cancer

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Abstract

Oral cancer is one of the most common cancers in the world. Drugs can modulate the expression of drug metabolizing enzymes and are useful in chemoprevention as well as therapy in cancer. 4-Nitroquinoline 1-oxide (4-NQO) is used to induce oral cancer in the present study. In the present investigation, the effect of green tea polyphenols (GTP) on the activities of cytochrome *b*5, cytochrome P450, cytochrome *b*5 reductase (cyt *b*5 R), cytochrome P450 reductase (cyt P450 R), arryl hydrocarbon hydroxylase (AHH), DT-diaphorase (DTD)(Phase I enzymes) and glutathione-*S*-transferase (GST) and UDP-glucuronyl transferase (UDP-GT) (Phase II enzymes) were assessed in tongue and oral cavity. In induced rats, there was a decrease in the activity of Phase II enzymes and an increase in the activity of Phase I enzymes. On supplementation of GTP by both simultaneous and post treatment mode (200 mg/kg) there was a significant increase in the activity of GST and UDP-GT and a significant decrease in the activity of Phase I enzymes. There was a significant decline in the number of tumors, tumor volume and oral squamous cell carcinoma in both simultaneous and post GTP treated animals relative to 4-NQO induced animals; on comparing simultaneous and post GTP treated animals the number of tumors, tumor volume and oral squamous cell carcinoma was significantly reduced in post treated animals. Thus inhibition of Phase I enzymes could be attributed to the protective efficacy of GTP which deactivates carcinogen and GTP induced the expression of Phase II enzymes that detoxifies the 4-NQO. It can be proposed that GTP plays role as a detoxifying agent by which its modulating role prevented/inhibited the formation of tumor.

Keywords: Drug metabolizing enzymes; Oral cancer; Green tea polyphenols; 4-Nitroquinoline 1-oxide; Detoxification; Oral squamous cell carcinoma

1. Introduction

Oral squamous cell carcinoma (SCC) is the most common malignancy of the head and neck, with a worldwide incidence of over 300,000 new cases annually. It is characterized by a high rate of morbidity and mortality

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(over 50%) and in those respects is similar to malignant melanoma [1]. The major inducer of oral SCC is exposure to tobacco, which is considered responsible for up to 90% of the cases worldwide and which may be responsible for the fact that this cancer is more prevalent in men. [2]. It is important to note that cigarette smoking has been identified as the chief avoidable cause of death in the United States [3]. The incidence of oral SCC in cigarette smokers is 4–7 times higher than in non-smokers, and when alcohol or chewing tobacco is added to the cigarette smoke the prevalence of the disease is increased by 19- and 123-fold, respectively [4]. In India, it is the leading cancer site in males constituting 19% of the total cancer cases, and is the third most common cancer in Indian females [5]. The etiology of oral and oropharyngeal cancers, in a majority of Indian oral cancer patients, is chewing tobacco, along with smoking and alcohol consumption, contributing to the high incidence of the cancer [6].

4-NQO is known to induce multistep carcinogenesis [7]. Therefore, it can serve as a good model to investigate oral carcinogenesis. The carcinogenic potential of 4-NQO is now well documented, and it has been shown to produce oral squamous cell carcinoma as well as spindle cell sarcoma in various rodent species [8]. Carcinoma is preceded by a sequence of hyperplasia-papilloma/dysplasia – carcinoma. 4-NQO is also known to induce H-ras mutation in chromosome 7 leading to head and neck squamous cell carcinoma in experimental murine model, which is quite similar to that of tumors that develop in tobacco chewers [9].

Most of the chemicals are not reactive themselves and require metabolic activation by a variety of enzymes responsible for drug metabolism to exert their genotoxicity. CYP is one of the major enzymes mainly involved in the activation of carcinogens [10]. Many of the p450 genes are known to exist in variant forms that have different activities. Since many carcinogens require metabolic activation before binding to DNA, individuals with an elevated metabolic capacity to activate specific carcinogens may be at an increased risk of cancer [11]. The balance between the CYP and GST enzymes therefore may substantially influence cancer risk [12].

Many chemopreventive agents have been shown to modulate gene expression including induction of Phase II detoxifying enzymes, such as GST and UDP-GT. Induction of Phase II enzymes in general leads to protection of cells/tissues against exogenous and/or endogenous carcinogenic intermediates. The antioxidant or electrophile response element (ARE/EpRE) found at the 5′-flanking region of these Phase II genes may play an important role in mediating their induction by xenobiotics including chemopreventive agents [13].

Recently, plant polyphenols have invited great interest because of their antioxidant capacity as well as their possible beneficial implications on human health, especially in the treatment and prevention of cancer [14]. One such chemopreventive agent is GTP. Green tea is a popular beverage consumed in some parts of the world and is a rich source of polyphenols, which are antioxidant in nature [15]. Green tea contains many polyphenols known as catechins, including epigallocathechin-3-gallate (EGCG), epigallocatechin (EGC) and epicathechin-3-gallate (ECG) [16]. In recent years, experimental studies have provided growing evidence for the beneficial action of GTP on multiple cancer-related biological pathways (carcinogen bioactivation, cell-signaling, cell cycle regulation, angiogenesis, oxidative stress and inflammation). Although the epidemiologic data on GTP and cancer are still limited and conflicting, some protective associations have been suggested for GTP [17]. Epidemiological studies have associated the consumption of green tea with a lower risk of several types of cancer including stomach, oral cavity, esophagus and lung. In fact, tea is one of the few agents that can inhibit carcinogenesis at the initiation, promotion and progression stages [17].

Srinivasan et al. previously studied the therapeutic effect of GTP on cellular thiols [18], glycoconjugates and immunological markers [19] against 4-NQO induced oral cancer. Most of the previous studies are on the chemoprevention by GTP and so the present study is directed to work on both chemoprevention as well as therapeutic effect of GTP on 4-NQO induced oral cancer by evaluating the modulating effect of GTP on Phase I and Phase II enzymes in 4-NQO induced oral cancer.

2. Materials and methods

2.1. Chemicals

4-NQO was purchased from Sigma Chemical Company, St. Louis, MO. Fresh green tea leaves were collected from ‘The Nilgris’. All other chemicals used were of analytical grade.

2.2. Green tea polyphenols

Fresh green tea leaves were collected from The Nilgris, India. Extraction of green tea polyphenols followed by Srinivasan et al. [18,19]. The extracted GTP was characterized using UV–vis spectrophotometer, infrared spectrophotometer and high pressure liquid chromatog-