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Dietary garcinol inhibits 4-nitroquinoline 1-oxide-induced tongue carcinogenesis in rats

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Abstract

The effects of dietary feeding with a polyisoprenylated benzophenone, garcinol, isolated from *Garcinia indica* fruit rind on the development of 4-nitroquinoline 1-oxide (4-NQO)-induced oral carcinogenesis were investigated in male F344 rats. At 7 weeks of age, animals were given 4-NQO at 20 ppm in the drinking water for 8 weeks to induce tongue neoplasms. They also received the diets containing 100 or 500 ppm garcinol either during (for 10 weeks) or after (for 22 weeks) the carcinogen exposure. The other rats were given tap water without 4-NQO throughout the experiment, and fed garcinol (500 ppm)-containing diet or basal diet alone. At the end of the study (week 32), incidences of tongue neoplasms and preneoplastic lesions, cell proliferation activity in the normal-like tongue epithelium estimated by 5-bromodeoxyurideine (BrdU)-labeling index and cyclin D1-positive cell ratio, and immunohistochemical expression of cyclooxygenase-2 (COX-2) in the tongue lesions were determined. Dietary garcinol significantly decreased the incidence and multiplicity of 4-NQO-induced tongue neoplasms and/or preneoplasms as compared to the control diet. Dietary administration of garcinol also significantly reduced the BrdU-labeling index and cyclin D1-positive cell ratio, suggesting reduction in cell proliferation activity in the tongue by garcinol. The COX-2 expression in the tongue lesions was also suppressed by feeding with garcinol. These results indicate that dietary administration of garcinol inhibited 4-NQO-induced tongue carcinogenesis through suppression of increased cell proliferation activity in the target tissues and/or COX-2 expression in the tongue lesions.

Keywords: Garcinol; Rat; Tongue cancer; 4-Nitroquinoline 1-oxide; Cyclooxygenase-2; Cyclin D1

Abbreviations: BrdU, 5-bromodeoxyurideine; CDK, cyclin dependent kinases; COX, cyclooxygenase; 4-NQO, 4-nitroquinoline 1-oxide; PG, prostaglandin; SCC, squamous cell carcinoma.

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1. Introduction

The incidence and the mortality of oral cancer, which is one of the important public health issues, have increased over the past decades in Europe [1] and in the United States [2]. Although Japan has one of the lowest incidences of oral, lip, and pharyngeal cancers in the world [3], the patients with these malignancies have recently been increasing [4]. Despite recent advances in surgery, chemotherapy, and radiotherapy, the survival of patients with oral carcinoma remains poor [1,2]. Furthermore, patients with oral cancer have an increased incidence of developing second primary tumors of the oral cavity [5,6]. The variation in the incidence of oral cancer in the world is related to exposure to known etiologic agents. It is generally believed that oral carcinomas are caused predominantly by chemical carcinogens, although there is evidence implicating viral, fungal, and physical stimuli in the genesis of some oral neoplasms. Tobacco and alcohol use and the combination of exposure to both are the major risk factors in the development of oral cancer and simultaneous or subsequent second primary cancers [5–10]. One promising approach to reduce the incidence and improve the prognosis of this malignancy is chemoprevention [11]. Dietary factors also play an important role in human health and in the development of certain chronic diseases including cancer [12,13]. Some foods contain antitumor compounds as well as mutagens and/or carcinogens [14]. Such compounds are candidates for chemopreventive agents against cancer development [15].

A polyisoprenylated benzophenone garcinol (Fig. 1, also named camboginol [16] is present in Guttiferae (*Garcinia indica*, *Garcinia huillkensis* and *Garcinia cambogia*). *Garcinia* is a rich source of secondary metabolites including xanthone and flavanoids. In India the dried fruit rind of *G. indica* ('Kokum') is used as a garnish for curry and in some of the folklore medicine and it contains a yellow pigment of garcinol (2–3%, w/w). Garcinol is known to have the same antioxidant property as other chemopreventive agents [17]. We previously reported a possible chemopreventive ability of garcinol in chemically induced colonic preneoplastic lesions in rats [18]. In addition, we demonstrated that garcinol suppresses expression of cyclooxygenase (COX)-2 proteins [18]. Overexpression of COX-2 and elevation of COX-2-mediated prostaglandin (PG) E_2 biosynthesis are involved carcinogenesis in certain organs including oral cavity [19–21].

One of the suitable animal models for field cancerization and for detecting cancer chemopreventive agents is 4-nitroquinoline l-oxide (4-NQO)-induced rat oral carcinogenesis model [22]. 4-NQO, a water-soluble quinoline derivative, produces a spectrum of preneoplastic and neoplastic lesions in the oral cavity, especially tongue, of rats following 4-NQO application in drinking water. Oral lesions produced by 4-NQO are comparable to human lesions, because many ulcerated and endophytic or exophytic tongue tumors and dysplasia develop when 4-NQO in the drinking water is given to rats or 4-NQO is applied topically to the oral mucosa [23]. Using 4-NQO-induced rat oral carcinogenesis model, we have reported several candidates for chemopreventive agents against oral malignancy [22].

In the current study, possible inhibitory effects of dietary exposure of garcinol during the initiation or post-initiation stages on 4-NQO-induced oral carcinogenesis were investigated in male F344 rats. In addition, the effect of the compound on cell proliferation activity in the tongue was assessed by measuring 5-bromodeoxyuridine (BrdU)-labeling index and cyclin D1-positive cells. The effect of the expression of COX-2 was slso immunohistochemically determined in the tongue lesions induced by 4-NQO.

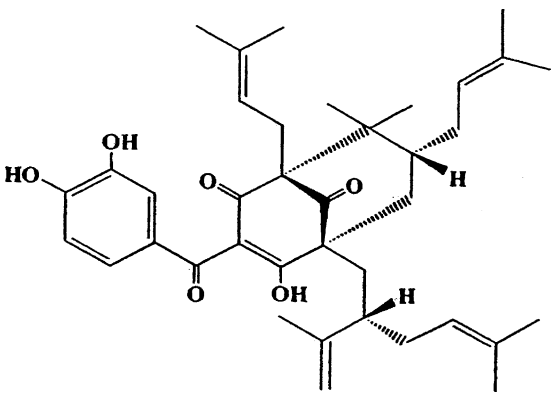

Fig. 1. Chemical structure of garcinol.