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REVIEW ARTICLE

Potential Cancer Chemopreventive Activity of Protocatechuic Acid

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A natural phenolic compound, protocatechuic acid (3,4-dihydroxybenzoic acid), is present in many edible and medicinal plants. Recent studies, including our animal experiments, indicate that this simple phenolic acid could be protective against the development of epithelial malignancy in different tissues and cardiovascular diseases as well. The mechanism of the action is mostly associated with antioxidant activity, including inhibition of generation as well as scavenging of free radicals and upregulating antioxidant enzymes. The influence on Phases I and II of the metabolism of certain carcinogens and, perhaps, direct blocking of specific binding sites of ultimate carcinogens with DNA molecule, thus preventing adduct formation that may result in mutations and neoplastic transformation, also account for its cancer protective action. However, other biological aspects of the chemopreventive activity of protocatechuic acid are not fully studied. They include influence on the activity of inducible isoenzyme of cyclooxygenase and nitric oxide synthase, cell cycle–regulating proteins, or inflammatory cytokines, which are involved in oncogenesis. In view of its reported biological properties and relative safety, protocatechuic acid is a potential cancer chemopreventive product.

1. Introduction

Prevention of chronic diseases, including cancer, is an old but important concept regarding human health. Dietary factors are known to influence cancer development.[1,2] An important consideration in cancer research today is that exposure to pharmacologically active chemicals (natural and synthetic) may play an important role in reducing the risk of cancer development.[1,3,4] Cancer chemoprevention could be possible by the use of exogenous factors to enhance endogenous mechanisms that reduce the risk of cancer development because of exposure to different environmental factors. Some of these exogenous factors are dietary constituents, drugs, immunizations, and supplements. Edible plants and plants used for folk medicine are rich sources of such cancer chemopreventive agents.[3–6]

Protocatechuic acid (3,4-dihydroxybenzoic acid; Figure 1) is a simple phenolic compound widely distributed in nature. Like many other simple phenolic acids, protocatechuic acid is detected in almost all plants and is, therefore, a very common component of human diet,[7] such as the bran and grain brown rice (*Oryza sativa* L.)[8] and onion (*Allium cepa* L.),[9] especially in the scales. Protocatechuic acid is detected in many fruits, such as plums (*Prunus domestica* L.)[10]; gooseberries (*Ribes uva-crispa* L.)[9]; grapes (*Vitis vinifera*)[11]; and nuts, such as almonds ordinary (*Prunus amygdalus*).[12] It is present in products of plant origin, such as olive oil or white wine.[13–15] Protocatechuic acid is also found in many plants and spices, such as star anise (*Illicium verum*), melisie (*Melissa officinalis* L.), a medical rosemary (*Rosmarinus officinalis* L.), and cynamonowcu (*Cinnamomum aromaticum*).[9] This compound is one of the biologically active components of some medicinal plants, including those used in natural medicine, such as sudan Mallow (*Hibiscus sabdariffa* L.),[16,17] Japanese ginkgo (*Ginkgo biloba* L.),[18] and St. John's wort (*Hypericum perforatum* L.).[19]

We demonstrated the chemopreventive ability of protocatechuic acid in chemically induced carcinogenesis in mainly the digestive organs of experimental animals.[20,21] In this review, we have highlighted the protective mechanisms of protocatechuic acid against carcinogenesis.

2. Effects of Protocatechuic Acid on Chemical Carcinogenesis in Rodents

The chemopreventive action of protocatechuic acid was evaluated in several models of chemically induced carcinogenesis in laboratory animals (Table 1).[16,22–33] The results indicate that the protocatechuic acid at doses of 200–2000 ppm in diet effectively inhibited the development of most of the cancers, especially of the digestive

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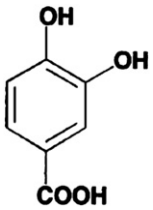

Figure 1 Chemical structure of protocatechuic acid (3,4-dihydroxybenzoic acid). Chemical abstracts service (CAS) No.: 99-50-3; Molecular weight (MW): 154.12.

system,[21] when administered both in the initiation phase and in the promotion/progression of carcinogenesis.

Efficacy of protocatechuic acid was demonstrated in the prevention of cancers of the oral cavity in several experimental models using rats and hamsters. Dietary feeding with protocatechuic acid during the initiation phase or the promotion/progression of tongue carcinogenesis of rats reduced the incidence and the number of preneoplastic lesions (hyperplasia and dysplasia) and epithelial neoplasms (squamous cell carcinomas and papillomas) induced by 4-nitroquinoline oxide.[22] A recent study with modified experimental protocol using the same carcinogen, which was able to cause a greater percentage of carcinomas in the advanced stage, has shown that treatment with protocatechuic acid in the progression phase reduced the incidence of precancerous lesions and cancers invading adjacent organs or metastatizing to the lungs.[23] Protocatechuic acid given during the promotion/progression of carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene in the cheek pouch of hamsters significantly reduced the size of tumors and the area occupied by a precancerous lesion, squamous cell dysplasia.[24]

In the model of rat colon carcinogenesis induced by azoxymethane, protocatechuic acid in diet during the initiation or promotion/progression lowered the number of aberrant crypt foci, which are considered to be putative precancerous lesions,[34–36] and the incidence and number of colorectal adenocarcinoma.[5,25,34]

Protocatechuic acid administered during promotion/progression of pancreatic carcinogenesis induced by *N*-nitrosobis(2-oxopropyl)amine in Syrian golden hamsters caused a significant reduction in the incidence of large pancreatic cancer (>3 cm) invading the adjacent organs.[26]

Protocatechuic acid also affected the development of neoplasia in the rat liver induced by diethylnitrosamine.[27] When protocatechuic acid was administered in diet during the initiation or promotion/progression phases of carcinogenesis, the incidence of altered hepatocellular foci, characterized by lack of iron accumulation and being positive for the reactivity against placental isoform of glutathione *S*-transferase (GST), was decreased. The treatment also reduced the multiplicities of both liver cell adenomas and carcinomas. Chemoprevention effects of protocatechuic acid in urinary bladder carcinogenesis was also revealed in rats initiated with *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine by the reduction of the incidence of precancerous lesions (hyperplasia and dysplasia) and cancers when rats were fed the diet containing the chemical during the initiation or promotion/progression stages.[28]

Our data on cancer chemopreventive ability of protocatechuic acid indicate that dietary administration with protocatechuic acid at 500 or 1000 ppm during the initiation and postinitiation stages suppresses chemically induced carcinogenesis in the tongue, glandular stomach, colon, liver, and urinary baldder of rats,[21,28] suggesting that 500 ppm is enough to inhibit the carcinogenesis in these tissues. In addition, we have found the protective effect of 2000 ppm of protocatechuic acid in diet against progression of tongue carcinogenesis.[23] Therefore, it is possible that less than 2000 ppm of this compound might inhibit all phases (initiation, promotion, and progression) of tongue carcinogenesis.

There are also reports showing negative chemopreventive activity of protocatechuic acid. In the experimental lung tumorigenesis of

Table 1 Evaluation of the activities of protocatechuic acid in preventing different chemical carcinogenesis in rodents

Species/strain/gender of animals	Carcinogen/promoter	Protocatechuic acid		Target tissue/cancer	Response	Authors/yr (ref. no.)
		Dose/rout	Experimental protocol			
F344 rats/males	4-NQO	500, 1000, 2000/in diet	4-NQO + PCA and 4-NQO → PCA	Oral cavity (tongue)/SCC	Inhibition	Tanaka T et al/1994[22]
F344 rats/males	4-NQO	2000/in diet	4-NQO → 4-NQO + PCA	Oral cavity (tongue)/SCC	Inhibition	Suzuki R et al/2003[23]
Syrian golden hamsters/males	DMBA	200 ppm/in diet	DMBA → PCA	Bucccal pouch/SCC	Inhibition	Ohnishi M et al/1997[24]
F344 rats/males	MNNG	1500 ppm/in diet	MNNG → PCA	Forestomach/SCC	No effects	Hirose M et al/1992[30]
F344 rats/males	AOM	1000, 2000 ppm/in diet	AOM + PCA → PCA	Colon/ADC	Inhibition	Kawamori T et al/1994[33]
F344 rats/males	AOM	250, 500, 1000 ppm/in diet	AOM + PCA and AOM → PCA	Colon/ADC	Inhibition	Tanaka T et al/1993[25]
Syrian golden hamsters/females	BOP	500, 1000 ppm/in diet	BOP → PCA	Pancreas/ADC	Inhibition	Nakamura H et al/2000[26]
F344 rats/males	DEN	500, 1000 ppm/p.o.	DEN + PCA and DEN → PCA	Liver/AD	Inhibition	Tanaka T et al/1993[27]
A/J mice/females	NNK	1000 ppm/in diet	NNK + PCA and NNK → PCA	Lung/AD	No effects	Mori H et al/1999[29]
F344 rats/males	BBN	500; 1000; 2000 ppm/in diet	BBN + PCA and BBN → PCA	Urinary bladder/TCC	Inhibition	Hirose Y et al/1995[28]
CD-1 mice/females	B[a]P/TPA	5, 10, 20 μM/locally on the skin 5 min before TPA	DMBA → TPA + PCA	Skin/PAP	Inhibition	Tseng TH et al/1998[16]
ICR mice/females	DMBA /TPA	16, 160, 1600 nM/topically to the skin 0; 40 min or 3 hr before TPA	DMBA → TPA + PCA	Skin/PAP	Inhibition (16nM); no effects (160nM and 1600nM) Enhancement of skin papilloma by 1600nM PCA	Nakamura Y et al/2000[32]
F344 rats	PhIP	2000 ppm /in diet	PhIP + PCA → PCA	Breast/ADC	No effects	Mori H et al/1999[31]

AD = adenoma; ADC = adenocarcinoma; AOM = azoxymethane; B[a]P, benzo[a]pyrene; BBN = *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine; BOP = *N*-nitrosobis(2-oxopropyl) amine; DEN = *N*-diethylnitrosamine; DMBA = 7,12 dimethylbenz[*a*]anthracene; MMMG = *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine; NNK = 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; 4-NQO = 4-nitroquinoline oxide; PAP = squamous cell papilloma; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; SCC = squamous cell cancer; TCC = transitional cell carcinoma; TPA = 12-*O*-tetradecanoylphorbol 13-acetate.