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Chemoprevention by Naturally Occurring and Synthetic Agents in Oral, Liver, and Large Bowel Carcinogenesis

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Abstract A number of naturally occurring compounds and several related synthetic agents were confirmed to exert chemopreventive properties against carcinogenesis in the digestive organs. Phenolic compounds, widely distributed as plant constituents, possess chemopreventive activities in tongue, liver, and large bowel of rodents. Of them, a simple phenolic protocatechuic acid seems to be a promising compound. Organosulfur compounds contained in the cruciferous vegetables and known to activate detoxifying enzymes are regarded as a candidate group for cancer preventive agents. We proved a strong protective effect of S-methylmethanethiosulfonate, a constituent in these vegetables, on azoxymethane (AOM)-induced large bowel carcinogenesis. Some oxygenated carotenoids (xanthophylls) are reported to have antitumor effects. Naturally occurring xanthophylls astaxanthin and canthaxanthin have considerable preventive activities on 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis and AOM-induced large bowel carcinogenesis. A novel synthesized retinoidal butenolide, KYN-54, which suppresses large bowel as well as tongue carcinogenesis, could be a useful agent for prevention of digestive organ cancers. Some trace elements are known to have anticarcinogenic effects. Magnesium hydroxide, a protective agent in colorectal carcinogenesis, inhibits c-*myc* expression and ornithine decarboxylase activity in the mucosal epithelium of the intestine. Our results show that many agents with preventive effects in tongue, liver, and large bowel control carcinogen-induced hyperproliferation of cells in these organs. Carcinogens used to induce large bowel cancers also induce apoptosis in the target sites. Telomerase activity is increased in the tissues of preneoplastic as well as neoplastic lesions in experimental models such as dimethylbenz[*a*]anthracene-induced oral carcinogenesis in hamsters. These could be useful biomarkers in studies for cancer chemoprevention. J. Cell. Biochem. Suppl. 27:35–41.

Key words: chemoprevention; tongue; liver; large bowel

Digestive tract epithelium is continuously exposed to substances taken orally, and liver metabolizes the absorbed agents. Thus, digestive organs could be where carcinogenesis is most strongly influenced by environmental agents. A variety of natural chemicals have been known to possess antioxidative, antimutagenic, or antineoplastic properties. Currently, these naturally occurring compounds are regarded as a promising chemical group for cancer prevention. Our group has demonstrated the intervening effects with a number of naturally occurring chemicals and related synthetic agents, using animal models for carcinogenesis in digestive organs [1]. We have clarified the mode of action of some chemopreventive agents. They included antioxidative properties or effects on cell proliferation [2]. Combining such properties makes possible the establishment of short-term assays for screening chemopreventive agents [3]. This report shows chemopreventive effects of naturally occurring chemicals, including phenolic compounds, organosulfur compounds and carotenoids, and some related synthetic chemicals, on oral, liver, or large-bowel carcinogenesis. Furthermore, new biomarkers that could be useful in studies for chemoprevention are also shown.

CHEMOPREVENTIVE AGENTS IN DIGESTIVE ORGANS

Phenolic Compounds

Chlorogenic acid is a phenolic compound widely distributed as a plant constituent. We have examined the modifying effect of chlorogenic acid in a hamster model using methylazoxymethanol (MAM) acetate and found that

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the phenolic compound has a protective effect for large bowel cancers [4]. Coffee beans are know to contain chlorogenic acid. Recently, we obtained data showing that coffee bean extracts with a high concentration of chlorogenic acid repressed carcinogen-induced formation of aberrant crypt foci (ACF) [2], one of the precursor lesions for colorectal neoplasms. The preventive effects of chlorogenic acid are suggested to relate to its antioxidative properties. Kasai et al., 1993 [5] reported that chlorogenic acid is a potent inhibitor of formation of 8-hydroxydeoxyguanosine generated by oxidative DNA damage. We also examined antioxidative activities of chemopreventive phenolic compounds in the assay using erythrocyte membrane ghost system, or the assay using rat liver cells, and confirmed that all tested phenolic compounds have inhibitory effects on the lipid peroxidation in both systems [2] (Fig. 1). Ellagic acid is also a popular phenolic compound contained in a variety of edible plants. We have shown the protective effect of this compound on hepatocarcinogenesis in rodents [6]. Related phenolic chemicals such as caffeic acid or ferulic acid are also known to act as electrophilic trapping agents. These phenolic compounds were found to have chemopreventive properties for oral cancers in the rat model with 4-nitroquinoline-1-oxide (4NQO) [7], indicating that such naturally occurring phenolic compounds are applicable for preventing human oral neoplasia. A simple phenolic acid, protocatechuic acid, a constituent of edible plants, fruits, and vegetables, is known as a natural antioxidant. Modifying effects of protocatechuic acid on carcinogenesis in the oral cavity, stomach, large intestine, or liver, respectively, were tried using rat models with 4-NQO, N-methyl-N-nitrosourea, azoxymethane (AOM) or diethylnitrosamine (DEN). The phenolic compound was found to be effective in all the digestive organs [8–11].

Organosulfur Compounds

Organosulfur compounds, prominent in a number of chemopreventive agents, are present abundantly in cruciferous vegetables. Their mode of action is to activate detoxifying enzymes. We have shown antioxidative activities with a number of organosulfur chemicals [2], which seems to relate to their preventing effects. We have shown that sinigrin has inhibitory effects on DEN-induced hepatocarcinogenesis and 4-NQO-induced oral carcinogenesis in rats [12,13]. Benzyl isothiocyanate (BITC) and benzyl thiocyanate (BTC) are also constituents of cruciferous vegetables, being present as their glucosinolate precursors. Both thiocyanate compounds exerted chemopreventive effects on carcinogenesis in liver and intestine [14,15]. Recently, we confirmed that methylmethanethiosulfonate (MMTS), a constituent of cruciferous vegetables, has a considerable protective effect on colon carcinogenesis in rats [16]. In this study, dietary exposure of MMTS at a concentration of 100 ppm during post-initiation phase was particularly effective on AOM-induced colorectal carcinogenesis (Table I). An inhibitory effect of this compound on DEN-induced hepatocarcinogenesis was also confirmed in our laboratory (unpublished data). Taurine, an organosulfur compound contained in a variety of animals and plants, has been reported to have antioxidative as well as antiatherosclerotic or antihypertensive effects. A chemopreventive effect of this chemical on large bowel neoplasms has been suggested [17], and we have proved a potent inhibitory effect of this agent on DEN and phenobarbital-induced hepatocarcinogenesis in rats [18].

Carotenoids and Related Chemicals

A number of carotenoids are present in nature, mostly as constituents of vegetables, fish, and sea algae. Beta carotene and carotenoids have been found to have some biological functions such as photoprotection and antioxidative properties, including singlet oxygen quenching. Some oxygenated carotenoids (xanthophylls) have been reported to possess antitumor effects. We have shown a protective effect of astaxanthin rather than canthaxanthin on bladder carcinogenesis in mice [19]. In subsequent studies, both xanthophylls were found to be effective for the prevention of 4-NQO-induced rat oral carcinogenesis [20] and AOM-induced large bowel carcinogenesis in rats [21]. Such chemopreventive effects of the oxygenated carotenoids may not depend on their provitamin A activity, but relate to their effectiveness as antioxidants and free radical scavengers. A novel retinoidal compound, 5-hydroxy-4-(2-phenyl-(E)-ethenyl)-2(5H)-furanone (KYN-54), was found to be chemopreventive of AOM-induced intestinal carcinogenesis [22]. This compound exerts effectiveness by exposure during post-initiation phase [23] as well as initiation phase [22]. Our recent study also indicated that this

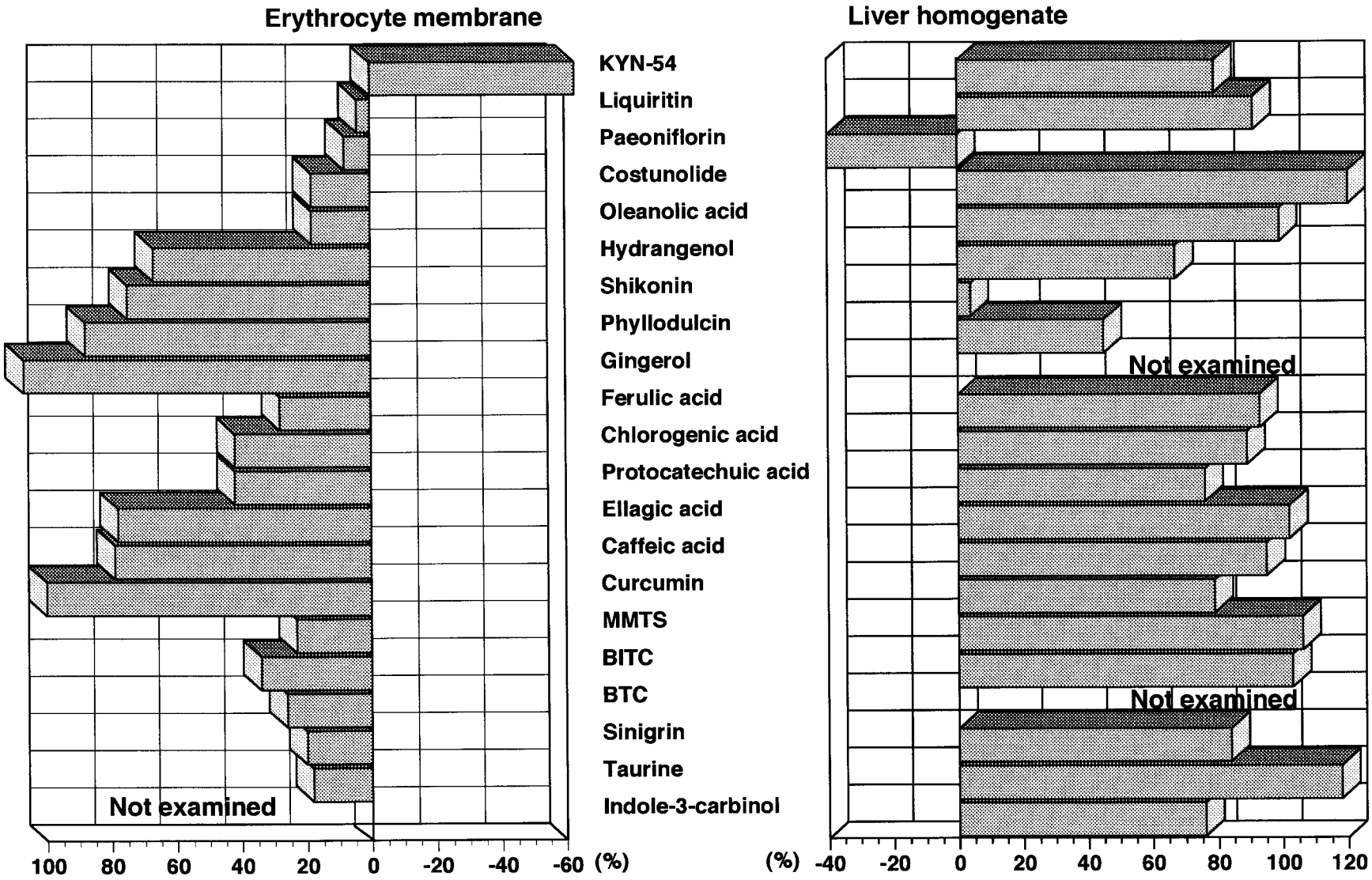

Fig. 1. Modifying effects of a number of agents on t-BuOOH or 2-nitropropane-induced lipid peroxidation (malon dialdehyde) in the erythrocyte membrane or liver homogenates. The data show the reduction rate (%) of the lipid peroxidation.

TABLE I. Incidences of Neoplasms in Large Intestine of Rats in Each Group

Group (treatment)	No. of affected rats	No. of rats with neoplasms (%)		
		Total	Adenoma	Adenocarcinoma
AOM alone	30	17 (57)	7 (23)	13 (43)
AOM + 20 ppm MMTS	24	9 (38)	4 (17)	6 (25)
AOM + 100 ppm MMTS	28	2 (7)*	2 (7)	0 (0)
Non-treatment	29	0 (0)	0 (0)	0 (0)

*Significantly different from the value of the group with AOM alone.

chemical is also effective in preventing oral carcinogenesis [24]. Arotinoids are retinoic acid analogs with improved anti-tumor effects without side effects. Among the arotinoids, mofarotene (Ro 40–8757) may show the most anti-tumor activity. We have proved that the arotinoid has a potent chemopreventive function on 4-NQO-induced oral carcinogenesis by concomitant exposure with the carcinogen [25].

Miscellaneous Compounds

A variety of naturally occurring compounds are included in plants used for Oriental medicine as well as food. Different chemicals contained in plant constituents for Oriental drugs have been tested for chemopreventive capability on intestinal neoplasia: flavoglaucin, a quinol fungal metabolite produced by *Aspergillus* used in the manufacture of popular flavoring for Japanese food; shikonin, a naphthoquinone having anti-inflammatory function; gingerol, an active compound in ginger; and costunolide, a sesquiterpene compound. All effectively prevented AOM-induced intestinal carcinogenesis in rats by exposure at initiation phase [26,27]. Plants contain micronutrients; trace elements such as selenium or calcium have been reported to have anticarcinogenic properties. Limited available information suggests the chemopreventive action of magnesium. We have demonstrated the inhibitory effect of magnesium hydroxide on MAM acetate or 1,2-dimethylhydrazine-induced large bowel carcinogenesis in rats [28]. The results of BrdU analysis [29] or PCNA labeling index, and expression of c-*myc* proto-oncogene [30] in mucosal epithelium, sug-

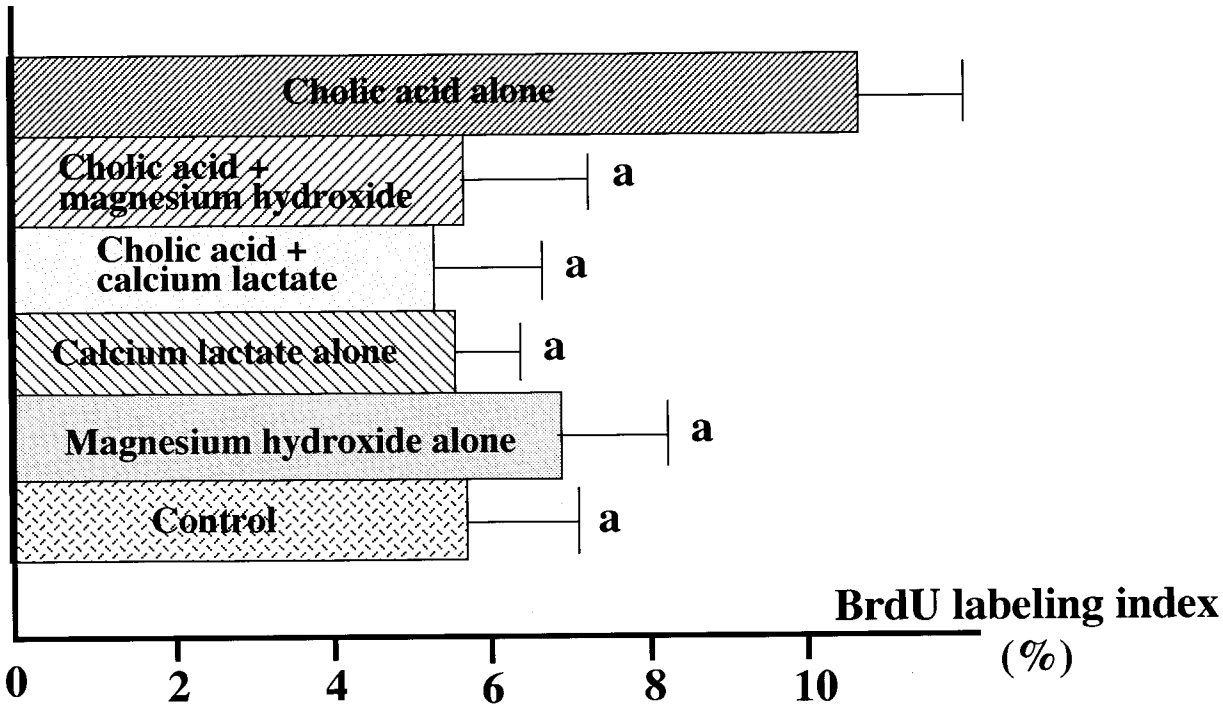

Fig. 2. Inhibitory effect of magnesium hydroxide on the bile acid-induced cell proliferation of colon epithelium in rats in comparison to the action of calcium lactate. Cholic acid, magnesium hydroxide, and calcium lactate were given for 8 weeks in the diet at a dose of 0.25, 0.2, and 1.18%, respectively. a: Significantly different from the value of rats with cholic acid alone ($P < 0.00001$).

TABLE II. Effects of Test Chemicals on Different Biomarkers in Rat Colons†

Group (treatment)	No. of ACF/colon	ODC activity	Polyamine concentration	No. of agnors/nucleus
AOM alone	152.5 ± 30.6	22.1 ± 19.4	6.79 ± 0.43	1.44 ± 0.28
AOM + phyllodulcin	139.1 ± 32.9	9.2 ± 7.1	6.22 ± 0.74	1.05 ± 0.27
AOM + hydrangenol	115.6 ± 30.7*	4.3 ± 6.9*	6.55 ± 0.45	1.05 ± 0.27
AOM + costunolide	118.6 ± 16.9*	0.6 ± 1.2*	5.42 ± 0.55*	0.88 ± 0.20*

†All values indicate mean ± SD.
*Significantly different from the value of the group with AOM alone.

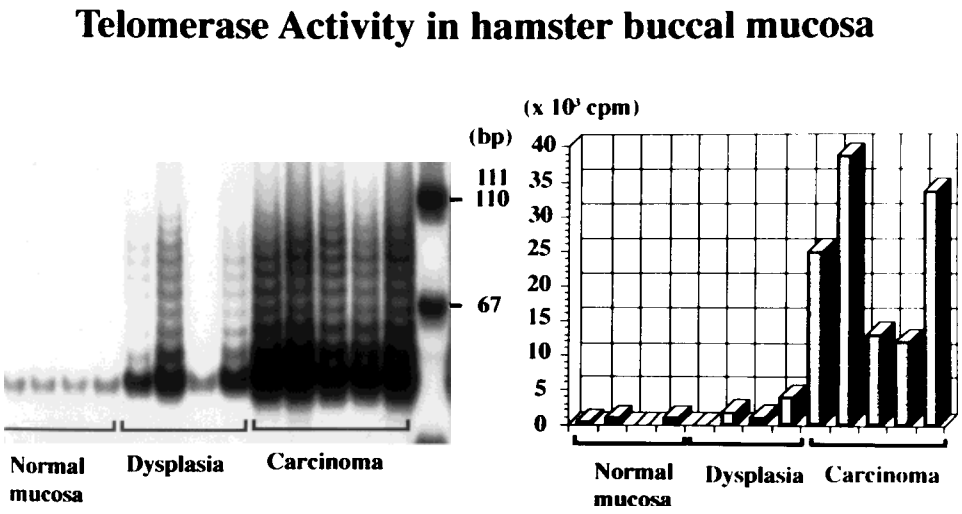

***Fig. 3.** Telomerase activity in 7,12-dimethylbenz(a)anthracene-induced hamster cheek pouch lesions. Telomerase expression is recognized in the tissues of dysplasia and carcinoma, and the order of the activity is carcinoma > dysplasia.

gested that the inhibitory effects of the trace element are related to control of carcinogen-induced hyper-proliferation of cells in mucosal epithelium. The modulating effects of magnesium hydroxide on epithelial cell proliferation in the rat colon caused by exposure of cholic acid were examined by measuring BrdU, and the data were compared with those of calcium lactate. The results indicated that magnesium hydroxide exhibits anticarcinogenic effects, as does calcium, by reducing increased cell proliferation of colonic epithelium generated by the toxic effects of bile acids [31] (Fig. 2). Nonsteroidal anti-inflammatory drugs (NSAIDs) are recognized as candidates for promising chemopreventive agents. It is known that NSAIDs inhibit COX2 enzyme, leading to prostaglandin biosynthesis, and induce apoptosis. In our study, the NSAID indomethacin strongly suppressed hydroxyanted carcinogenesis in rats [32], providing a possible experimental model for colitis-associated colorectal carcinogenesis, in which the activity of COX2 enzyme or cytokines like TNF-α or IL-1α is increased [33,34]. Chlorophyllin, the man-made sodium-copper salt of chlorophyll used to treat several human ailments and as a food additive, is also known to have antimutagenic activities [35]. Very recently, we proved that this agent has a chemopreventive effect on hepatocarcinogenesis in rodents [36]. Such chemicals may be promising preventive agents for human liver neoplasia.

SHORT-TERM ASSAYS FOR SCREENING CHEMOPREVENTIVE AGENTS AND POSSIBLE NEW BIOMARKERS

To detect chemopreventive agents, long-term carcinogenesis needs to be carried out. Establishing effective short-term assays to screen chemopreventive agents is desirable, and suitable assays will also contribute to analysis of mode of actions of each agent. In this context, reliable intermediate biomarkers are necessary, and some premalignant lesions such as altered hepatocellular foci or ACF are now regarded together with cell proliferation as proper

biomarkers. Meanwhile, cell proliferation is an important process of carcinogenesis, especially in digestive tracts [37]. We have proved that a variety of chemopreventive agents control carcinogen-induced hyper-proliferation of cells in the target organs by exposure during the initiation as well as the post-initiation phase. Accordingly, we conducted a short-term assay for screening chemopreventive agents, using combinations of different biomarkers like ACF, polyamine concentration, score of silver-stained nucleolar organizer region protein (AgNOR), or ornithine decarboxylase (ODC) activity [38]. Data from this assay for some naturally occurring agents used as oriental medicines are shown in Table II. In the assay, compounds such as costunolide indicated good scores in the expression of ACF and other biomarkers for cell proliferation. In fact, the chemopreventive effect of costunolide on large bowel carcinogenesis is also demonstrated in our laboratory [27]. Recently, we found that apoptosis occurs very fast in the mucosal epithelium for the target sites on AOM-induced colorectal carcinogenesis [39]; in vivo pretreatment with disulfiram, an inhibitor of oxidation in the metabolism of AOM, strongly suppressed AOM-induced apoptosis in the colons of rats [3]. Such biological events seen in the large bowel may be regarded as useful biomarkers for screening chemopreventive agents. Furthermore, increased telomerase activity was confirmed in the premalignant as well as malignant lesions on 7,12-dimethylbenz[*a*]anthracene-induced buccal pouch carcinogenesis in hamsters. The order of the strength of the telomerase activity was dysplasia < squamous cell carcinoma [40] (Fig. 3). These properties confirmed in the animal model for carcinogenesis could be useful in the experimental study of cancer prevention.

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