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Polyphenolic Phytochemicals as Colorectal Cancer Chemopreventive Agents: An Intelligent Alternative to NSAIDs?

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Abstract: To review the evidence for using of polyphenolic phytochemicals as cancer chemopreventive agents. A literature search was undertaken from 1963 to the present day, using Medline and Pubmed. Epidemiological data suggests that diets rich in polyphenols confer significant protection against the risk of colorectal cancer. These observations are supported by *in vitro* and *in vivo* data. Polyphenols are polymechanistic in their anti-cancer action, but a common mechanism to all is their anti-oxidant property. Poor bioavailability, however, is potentially a limiting factor to their further development as clinical agents. Data regarding the chemopreventive efficacy of polyphenolic compounds is growing. Clinical trial data, although limited, suggests that such compounds show great potential for use as chemopreventive agents. The poor bioavailibity of polyphenols could be advantageous in achieving a localised therapeutic effect in the gastrointestinal tract, thus minimising the risk of unwanted effects in organs distant from the locus of absorption.

Key words: Polyphenols, colorectal cancer, chemoprevention

INTRODUCTION

Colorectal cancer is the second most common cause of cancer death in the western world. Efforts to reduce mortality from this disease are currently focussed on early detection of precursor lesions and polyps and early diagnosis of established cancers. Other health strategies include chemoprevention, using either synthetic drugs or naturally occurring agents, that interfere with the multi-step pathway of carcinogenesis]. Chemoprevention can be applied in three different scenarios. Primary chemoprevention entails administering a chemopreventive agent to the general population regardless of individual risk. Secondary chemoprevention involves a more focussed intervention where populations with an inherited or familial risk are targeted and tertiary chemoprevention selects populations following resection of a colorectal cancer, in an attempt to reduce the risk of local recurrence or metastatic spread[1].

Recent randomised clinical trials have shown that Non-steroidal Anti-inflammatory Drugs (NSAIDs) such as the relatively non-selective Cyclooxygenase (COX) inhibitors, piroxicam and sulindac and the relatively selective COX-2 inhibitor, celecoxib, are able to cause regression of adenomas in patients with familial adenomatous polyposis, by up to 100%[2-5]. The administration of aspirin to patients with recurrent colonic adenomas, or previous colorectal cancer, has also been shown to reduce new polyp formation by up to 35%[6,7]. The structures of common NSAIDs can be seen in Fig. 1. Such studies suggest that chemoprevention could become a clinical reality, although to be effective patients would be required to take these drugs for many years. It is well documented that long term administration of NSAIDs such as aspirin is associated with side-effects

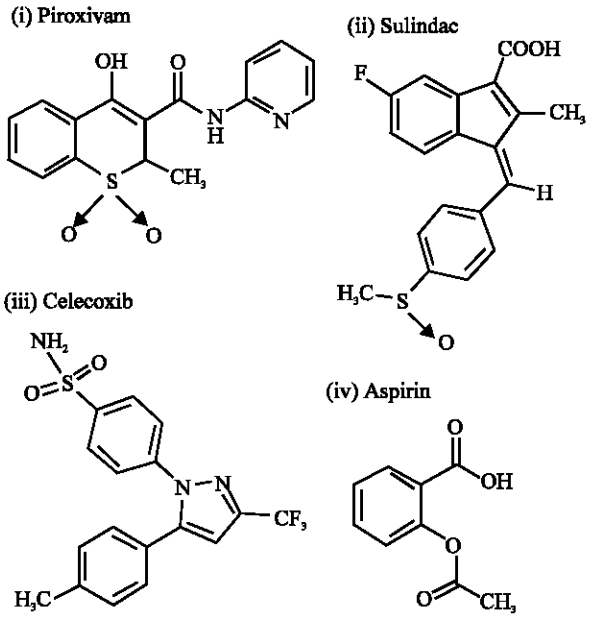

Fig. 1: Structures of common NSAIDs

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such as gastric mucosa inflammation, bleeding, dyscrasias, gastric ulceration and renal impairment. The inevitable morbidity associated with such side-effects may obfuscate any benefit gained from reduction of colorectal cancer risk. The recent worldwide withdrawal of the COX-2 inhibitor, Rofecoxib, further highlights the potential problems of long -term NSAID use. In this short report, evidence is reviewed that supports the notion of polyphenolic phytochemicals being considered an efficacious and safe alternative to NSAIDs.

Why polyphenolic phytochemicals?: Polyphenolic phytochemicals make up a large proportion of the constituents of the human diet, the main sources being fruits, chocolate, vegetables, cereals, legumes and beverages such as tea, coffee and wine[8]. The exact classification and definition of polyphenolic compounds is open to debate and not the focus of this review. This report will centre mainly on three compounds namely curcumin, the major yellow pigment in the spice turmeric, resveratrol, a component of grapes and red wine and tea polyphenols with particular emphasis on epigallocatechin gallate (EGCG) (Fig. 2).

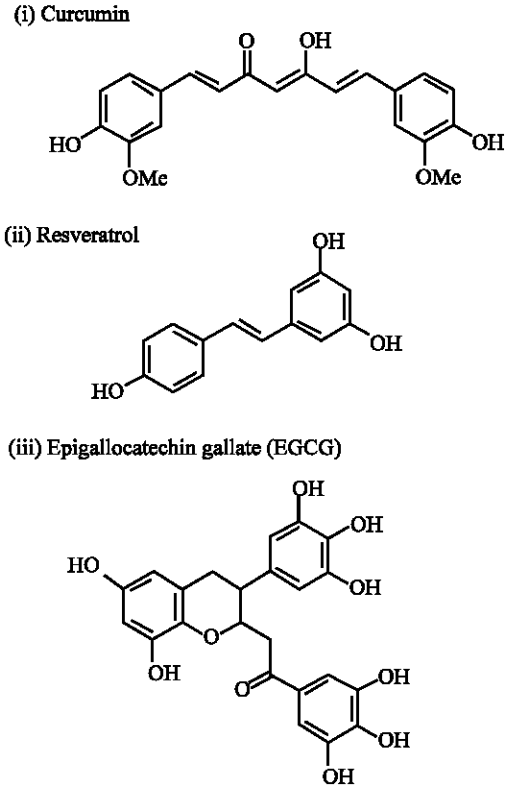

Fig. 2: Structures of a number of common polyphenolic phytochemicals

The conception that polyphenolic phytochemicals possess colorectal cancer chemopreventive properties is based on epidemiological findings that suggest the intake of polyphenol rich foods may delay the onset of cancer via antioxidant activity, induction of phase I and II detoxifying systems or by preventing the formation of carcinogenic precursors, such as heterocyclic amines[9]. More recently there is evidence to suggest that certain polyphenols have a direct inhibitory effect on cancer cell growth by inhibiting proliferation, promoting apoptosis and inhibiting angiogenesis[10,11]. Observational and case-control studies indicate that intake of fruit and vegetables is associated with a lower risk of colorectal cancer[12-18]. The protective effect of high fruit intake is also evident amongst cohorts of individuals who are at high risk of colorectal cancer, including those with previous cancer history, colonic polyps and ulcerative colitis[19]. Several retrospective epidemiological studies have shown that regular ingestion of green tea can be chemopreventive[20-23]. One large Japanese study followed 8552 patients over a nine-year period and observed an average delay of cancer onset of 4 years ($p<0.01$) in individuals who consumed 10 or more cups of green tea daily, when compared to those consuming less than 3 cups daily[24].

Mechanisms of NSAID-and Polyphenolic Phytochemical-Mediated Cancer Chemopreventive Activity: A wide range of polyphenolic agents have been identified and are currently under evaluation using *in vitro* and *in vivo* models of carcinogenesis. To fully understand the potential of these polyphenolic phytochemicals, we must understand how they exert chemopreventive activity. Some of the known mechanisms of NSAID-and polyphenol-mediated chemopreventive activity are outlined in Table 1 and 2, respectively. These data show that both groups of compounds act *via* multiple mechanistic pathways, some of which overlap, for example antioxidation. The exact mechanistic pathways associated with cancer chemopreventive effects are, as yet, unclear. Some of the potential chemopreventive mechanisms associated with curcumin, green tea and resveratrol will now be considered.

Curcumin is a bright yellow pigment derived from the rhizome *Curcuma* Longa (Fig. 2 for chemical structure). It is found in the spice turmeric, which is widely used in Indian cuisine as a colouring and flavouring. Like many polyphenols curcumin has been shown to inhibit COX-2 expression in both human colorectal tumour cell lines *in vitro*[25] and to decrease PGE-2 expression in humans *in vivo*[26]. Curcumin has been shown to inhibit oxidative DNA adduct formation as measured by levels of the

Table 1: Mechanistic targets of NSAIDs potential related to cancer chemoprevention

Therapeutic target	Compound
COX-1 and / or COX 2 inhibition	Piroxicam
	Aspirin
	Sulindac
	Celecoxib (COX-2 only)
Induction of apoptosis	Piroxicam
	Aspirin
	Sulindac
Modulation of LOX	Piroxicam
	Aspirin
	Sulindac
Suppression of prostaglandin synthesis	Piroxicam
	Aspirin
	Sulindac
	Celecoxib
Induction of cell cycle arrest	Celecoxib
	Sulindac
Inhibition of angiogenesis	Aspirin
	Celecoxib

Table 2: Mechanistic targets of polyphenolic phytochemicals potentially related to cancer chemoprevention

Therapeutic target	Compound
COX-2 inhibition	Curcumin
	Black tea
Induction of apoptosis	Curcumin
	Epigallocatechin gallate
Immune system modulation	Curcumin
	Resveratrol
Inhibition of cell signalling pathway via cyclin D1	Resveratrol
Induction of GST Phase II detoxifying enzymes	Resveratrol
	Curcumin
Inhibition of nitric oxide synthase	Black tea extract
	Curcumin
	Resveratrol
Inhibition of oxidative DNA adduct formation	Black tea extract
	Curcumin
Anti-oxidant mechanism	Curcumin
	Resveratrol
	Green tea extract
	Black tea extract

pyrimidopurinone DNA-adduct (M_1G)[27], decrease the expression of the onco-protein beta-catenin[28], induce apoptosis in Colo 320 colon cancer cells and AOM-induced colon tumors[29,30] and induce the glutathione-S-transferase (GST) de-toxification enzyme system[27,31]. Curcumin can also modulate immune system-mediated tumour cell killing by increasing the numbers of intestinal CD4+ T cells and B cells[32].

Resveratrol is a polyphenolic compound found in grapes, peanuts, berries and red wine (Fig. 2 for chemical structure). Experiments using cancer cell lines *in vitro* have shown resveratrol has an anti-proliferative effect[33,34] and in $CaCo_2$ human colon cancer cells, resveratrol induced the accumulation of cells in the S/G2 phase of the cell cycle, reflected by a 70% inhibition of growth[35]. Similarly in HT29 colon adenocarcinoma cells, resveratrol induced cell cycle arrest at the G2 phase *via* inhibition of CDK7 kinase activity[36]. Resveratrol can also preferentially alter the levels of proteins involved in apoptotic pathways. For example, in $CaCo_2$ colon cancer cells, high concentrations of resveratrol activated the proapoptotic protein caspase-3[37]. In HCT116 cells resveratrol has been shown to activate a p53-independent apoptotic pathway that is potentially linked to cell differentiation[38] and to induce both Bax-mediated and Bax-independent mitochondrial apoptosis[39].

Green tea contains a number of polyphenolic phytochemicals known as catechins. Epigallocatechin gallate (Fig. 2), one of the primary catechins, has been shown to induce apoptosis and interfere with cell cycle progression in a number of colorectal tumour cell lines *in vitro*[40-43]. This cytostatic effect was specific to tumour cells alone. Other effects include inhibition of DNA adduct formation[44], preservation of the colonic microflora[45] and electrophile scavenging[46]. Epigallocatechin Gallate (EGCG) has been shown to inhibit DNA topoisomerase I, an enzyme involved in cell survival and DNA metabolism and structure, in numerous human colon carcinoma cell lines[47]. Tea polyphenols have also been shown to induce enzymes involved in Phase II detoxification of dietary carcinogens[48].

With regard to chemoprevention mediated by NSAIDs, it is thought that inhibition of COX-2 activity is an important mechanism of action in colorectal cancer, however, other mechanisms are documented (Table 1) and include modulation of apoptosis, induction of cell-cycle arrest and inhibition of angiogenesis[10,11]. Furthermore, sulindac has been shown to modulate the β-catenin/TCF4 pathway *via* induction of p21 expression[49] and celecoxib can decrease phorbol-ester-induced COX-2 expression and AP-1 DNA binding[50] and can inhibit NF-κB activation[51].

Chemopreventive efficacy of polyphenolic phytochemicals and NSAIDs *in vivo*: The data demonstrate that there is a degree of overlap between the mechanisms of chemopreventive activity of polyphenols and NSAIDs and support the notion that polyphenols are effective chemopreventive agents. But an important consideration is the relative efficacy of polyphenols as chemopreventive agents when compared to NSAIDs *in vivo*.

Studies using genetic models of cancer and carcinogen-induced aberrant crypt foci models suggest that under certain conditions the chemopreventive efficacy of polyphenolic phytochemicals and NSAIDs can be similar (Fig. 3). Indeed, polyphenols such as green tea and soy appear to be more effective than NSAIDs at inhibiting carcinogen-induced ACF *in vivo*. The chemopreventive activity of NSAIDs and polyphenols against carcinogen-induced tumour models *in vivo* are compared in (Fig. 4). These data demonstrate that under

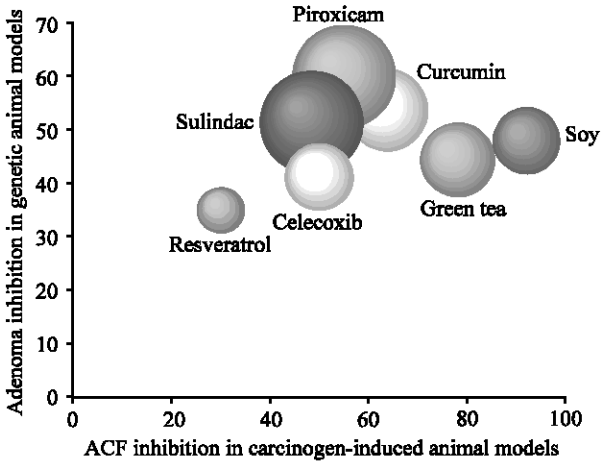

Fig. 3: Comparison of efficacy of NSAIDs and polyphenols in genetic animal models and carcinogen-induced cancer models. Bubble size relates to the number of studies evaluating that particular agent

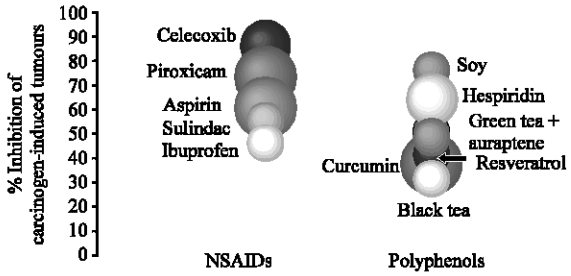

Fig. 4: Comparison of NSAIDs and polyphenols, ranked on potency to inhibit carcinogen-induced tumours. Bubble sizes relate to number of studies evaluating that particular agent

certain conditions NSAIDs such celecoxib can be more effective than polyphenols, although overall both groups of compounds show a similar range of efficacy.

Table 3-5 summarize the current *in vivo* data comparing the chemopreventive effects of curcumin, resveratrol and tea polyphenols to the those of the NSAIDs, piroxicam, sulindac and celecoxib in the $Apc^{Min/+}$ mouse, a model of human familial adenomatous polyposis and the azoxymethane (AOM)-induced adenocarcinoma rat model. Briefly, studies in the $Apc^{Min/+}$ mouse have shown that curcumin and resveratrol can inhibit adenoma formation by up to 70% in the small intestine and 100% in the colon[28,52]. Similar studies using NSAIDs have shown up to 99% inhibition of adenoma formation[53-62]. These data suggest that, depending on the dose and duration of treatment, curcumin and resveratrol are almost as effective as NSAIDs at inhibiting adenoma development. In studies

Table 3: Chemopreventive activity of NSAIDs and polyphenolic phytochemicals in the ApxMin/+ mouse. Treatment efficacy has been determined by inhibition of adenoma development

Compound	Dose (ppm)	Duration (days)	Adenoma development inhibition (%)	Reference
Piroxicam	25-220	7-180	34-95	[53-56, 60]
Sulindac	30-300	7-80	32-99	[53, 57-62, 94]
Celecoxib	150-1500	25-55	27-71	[55]
Curcumin	1000-2000	70-75	6-64	[28, 73, 95]
Resveratrol	100 (in water)	49	70	[52]
Tea extract	1000	70	22	[61]

Table 4: Inhibition of aberrant crypt formation following dietary intervention with NSAIDs and polyphenolic phytochemicals in the AOM-induced colon carcinoma rodent model.

Compound	Dose (ppm)	ACF development inhibition (%)	Reference
Piroxicam	75-400	38-70	[96-99]
Sulindac	100-320	36-53	[98, 100-103]
Celecoxib	1500	41	[101]
Curcumin	2000	42-57	[64, 67, 104]
Resveratrol	200	38	[105]
Tea extract	200-1200	35-57	[63, 66]

Table 5: Decrease of tumour incidence following dietary intervention with NSAIDs and polyphenolic phytochemicals in the AOM-induced colon carcinoma rodent model

Compound	Dose (ppm)	Decrease of tumour incidence (%)	Reference
Piroxicam	200-400	64-85	[106-108]
Sulindac	320	55	[109]
Celecoxib	1500	78-93	[110, 111]
Curcumin	600-40000	25-42	[112-114]
Tea extract	1000	51	[115]

using the AOM-induced adenocarcinoma rat model, curcumin and green tea extracts showed similar efficacy to NSAIDs at inhibiting aberrant crypt foci formation, although NSAIDs were superior at reducing tumour incidence[63-68].

Combined with the apparent lack of unwanted side effects following long term administration, these data suggest that certain polyphenolic phytochemicals may prove a sensible alternative to NSAIDs for use in colorectal cancer chemoprevention.

Bioavailability of polyphenolic phytochemicals: It is known that NSAIDs show a relatively high bioavailability. For example, aspirin is a weak acid that remains largely unionised in the acid environment of the stomach thereby facilitating its absorption[69]. Current preclinical data from *in vivo* models suggests that polyphenols are poorly absorbed and avidly metabolised. Small polyphenols such as caffeic acid are most bioavailable following oral administration showing up to 27% recovery from urine, whereas tea polyphenols are poorly bioavailable showing around 0.00006% recovery from urine[70]. Curcumin is poorly bioavailable and is subject to a rapid first pass metabolism[71] with only trace amounts detectable in the

peripheral circulation following oral administration[72,73]. Similarly other polyphenols such as resveratrol display poor bioavailability[74-76]. A further reduction in polyphenol bioavailability can also occur *via* bacteria-mediated degradation in the large bowel[8,77].

Polyphenols can conjugate with glucuronide moieties and such conjugation may assist in their absorption from the small intestine[78]. In an attempt to increase absorption and consequently bioavailability, polyphenols have been co-administered with compounds such as lipids and emulsifiers[79]. Such a protocol significantly enhanced the absorption of the polyphenol quercetin and might therefore prove beneficial to other polyphenolic agents. The co-administration of curcumin with a pepper constituent has also been shown to increase curcumin absorption by a factor of 20[80].

Certain polyphenols, such as epigallocatechin gallate from green tea, are excreted in bile[81]. Enterohepatic recirculation of bile excreted metabolites, a process that has been postulated following administration of resveratrol to rats[75], might act to sustain therapeutic drug concentrations in the gut following oral administration and may therefore potentiate chemopreventive activity. It should be noted that the major metabolites of polyphenols and their intrinsic chemopreventive efficacy are still largely uncharacterised. It is possible that the beneficial effects of polyphenols are not reliant on their absorption though the gut barrier and that their efficacy may result from a direct anti-oxidative effect on mucosal cells[82], beneficial effects on gastrointestinal micro-flora[83], localised absorption and distribution to gastric epithelial cells, or may be attributable to their metabolites.

The differences in bioavailability of certain NSAIDs and polyphenols do not appear to affect their chemopreventive efficacy in the gastrointestinal tract, for example the bioavailability of curcumin is poor, however, in the $Apc^{Min/+}$ mouse has shown considerable efficacy (Table 3). Although poor absorption of polyphenols is likely to hinder their chemopreventive activity in cells distant from the gastrointestinal tract, such limitations may result in localised accumulation in the gastrointestinal tract thereby dramatically decreasing the risk of untoward side-effects in distant organs.

Clinical studies of polyphenolic phytochemicals: As yet few polyphenolic phytochemicals have been investigated in clinical trials. Curcumin has thus far been the most investigated. Serum levels of curcumin have been shown to be low following oral administration to patient volunteers, with measured levels of <0.03 μM following doses of up to 2 g[80] and 1.75 μM after 8 g oral administration[84]. In one study, no detectable levels of curcumin were found in urine or blood following oral administration to human volunteers at doses from 36-180 mg[72], however, curcumin sulphate was detected in the faeces of one patient at the 180 mg dose level, thus supporting previous work showing polyphenol conjugation can occur in the gastrointestinal tract[85].

Clinical data suggest that curcumin is non-toxic and does not accumulate within the body. Daily oral doses as high as 8 g have been administered to patients for 3 months with no adverse effects[84] and other studies involving curcumin administered at doses of 180 mg to 200 mg daily failed to demonstrate any toxicity[72]. In a recent clinical trial[26] a daily 3.6 g dose of curcumin for 7 days resulted in curcumin accumulation in colorectal tissue to concentrations equivalent to those (5-5 μM) required for pharmacological activity in cells *in vitro*[25,86-90]. This same study[26] also found that patients receiving 3.6 g of curcumin had a significant reduction in tumour levels of oxidative DNA damage ($p<0.05$, student t test) and trace levels of curcumin were only detected in the peripheral circulation one hour after administration of the highest dose. These data show that despite its poor absorption and rapid elimination from the body, pharmacologically active levels of curcumin can be achieved in the colorectal mucosa when administered at high enough doses.

Clinical studies using green tea are relatively limited. The administration of standardised green tea solids (0.6-1.8 g), dissolved in warm water, to human volunteers has been shown to result in a rapid decrease of rectal mucosa PGE_2 levels within 8 h of consumption[91]. Unfortunately, the clinical use of such a regimen may be marred by reports of side-effects including bloating, nausea, vomiting, agitation, dizziness and restlessness[92]. Such side-effects are probably due to the caffeine content within green tea, often up to 7%[92]. Decaffeination is therefore an option, however, caffeine has been reported to enhance the chemopreventive efficacy of green tea[93] and removing it may reduce efficacy.

Recent data suggests that polyphenolic phytochemicals possess colorectal chemopreventive properties in both *in vitro* and *in vivo* models of colorectal carcinogenesis. Indeed, under certain conditions polyphenolic phytochemicals have been shown to be as effective as NSAIDs. The major confounding factor in the development of polyphenols as chemopreventive agents is their poor bioavailability. Although pharmacologically active concentrations are achievable in the intestinal mucosa, the dose required to achieve this may prove unpalatable to patients needing to be maintained on the medication for many years. The poor bioavailability of polyphenolic phytochemicals may,

however, prove to be a great asset. Although, limiting their use solely to the chemoprevention of colorectal cancer, the restriction of polyphenols to the gastrointestinal tract is likely to decrease the risk of untoward side-effects in organs distant to the locus of absorption. It remains to be seen if randomised clinical trials show polyphenols to be less, similarly, or more effective than NSAIDs in human colorectal cancer. The vast number of available polyphenols makes their development into clinical drugs a daunting but exciting project.

REFERENCES

1. Wattenburg, L., 1996. Chemoprevention of carcinogenesis: A Review. Cancer Res., 24: 1520-1526.
2. Nugent, K.P., K.C. Farmer, A.D. Spigelman, C.B. Williams and R.K. Phillips, 1993. Randomised controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br. J. Surg., 80: 1618-1619.
3. Labayle, D., C. Fisher and P. Viehl, 1991. Sulindac causes regression of rectal polyps in familiar adenomatous polyposis. Gastroenterology, 101: 635-639.
4. Giardiello, F.M., S.R. Hamilton and A.J. Krush, 1993. Treatment of colonic and rectal admonmas with sulindac in familiar adenomatous polyposis. New England J. Medicine, 328: 1313-1316.
5. Steinbach, G., P.M. Lynch and R.K. Phillips, 2000. The effect of celecoxib, a cyclooxygenase-2 inhibitor in familial adenomatous polyposis. New England J. Medicine, 342: 1946-1952.
6. Sandler, R.S., S. Halabi, J.A. Baron, S. Budinger, E. Paskett, R. Keresztes, N. Petrelli, J.M. Pipas, D.D. Karp, C.L. Loprinzi, G. Steinbach and R. Schilsky, 2003. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. New England J. Medicine, 348: 883-890.
7. Baron, J.A., B.F. Cole, R.S. Sandler, R.W. Haile, D. Ahnen, R. Bresalier, G. McKeown-Eyssen, R.W. Summers, R. Rothstein, C.A. Burke, D.C. Snover, T.R. Church, J.I. Allen, M. Beach, G.J. Beck, J.H. Bond, T. Byers, E.R. Greenberg, J.S. Mandel, N. Marcon, L.A. Mott, L. Pearson, F. Saibil and R.U. van Stolk, 2003 A randomized trial of aspirin to prevent colorectal adenomas. New England J. Medicine, 348: 891-899.
8. Scalbert, A., C. Morand, C. Manach and C. Remesy, 2002. Absorption and metabolism of polyphenols in the gut and impact on health. Biomedicine and Pharmacotherapy, 56: 276-282.
9. Dashwood, R.H., 2002 Modulation of heterocyclic amine-induced mutagenicity and carcinogenicity: An "A-to-Z" guide to chemopreventive agents, promoters and transgenic models. Mutation Res., 511: 89-112.
10. Thun, M.J., S.J. Henley and C. Patrona, 2002. Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic and clinical issues. J. Natl. Cancer Inst., 94: 252-266.
11. Chan, T.A., 2002 Nonsteroidal anti-inflammatory drugs, apoptosis and colon-cancer chemoprevention. Lancet Oncology, 3: 166-174.
12. Terry, P., E. Giovannucci, K.B. Michels, L. Bergkvist, H. Hansen, L. Holmberg and A. Wolk, 2001. Fruit, vegetables, dietary fiber and risk of colorectal cancer. J. Natl. Cancer Inst., 93: 525-533.
13. Sandler, R.S., 1996. Epidemiology and risk factors for colorectal cancer. Gastroenterol. Clin. North America, 25: 717-735.
14. Slattery, M.L., T.D. Berry, J. Potter and B. Caan, 1997. Diet diversity, diet composition and risk of colon cancer United States. Cancer Causes Control, 8: 872-882.
15. Voorrips, L.E., R.A. Goldbohm, G. van Poppel, F. Sturmans, R.J. Hermus and P.A. van den Brandt, 2000. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands cohort study on diet and cancer. American J. Epidemiol., 152: 1081-1092.
16. Franceschi, S., 1999. Nutrients and food groups and large bowel cancer in Europe. European J. Cancer Prevention, 8: S49-52.
17. Franceschi, S., A. Favero, C. La Vecchia, E. Negri, E. Conti, M. Montella, A. Giacosa, O. Nanni and A. Decarli, 1997. Food groups and risk of colorectal cancer in Italy. Intl. J. Cancer, 72: 56-61.
18. Deneo-Pellegrini, H., E. De Stefani and A. Ronco, 1996. Vegetables, fruits and risk of colorectal cancer: A case-control study from Uruguay. Nutrition and Cancer, 25: 297-304.
19. Matthew, J.A., I.W. Fellows, A. Prior, H.J. Kennedy, R. Bobbin and I.T. Johnson, 1997. Habitual intake of fruits and vegetables amongst patients at increased risk of colorectal neoplasia. Cancer Lett., 114: 255-258.
20. Ji, B.T., W.H. Chow, A.W. Hsing, J.K. McLaughlin, Q. Dai, Y.T. Gao, W.J. Blot and K.F. Jr. Fraumeni, 1997. Green tea consumption and the risk of pancreatic and colorectal cancers. Intl. J. Cancer, 70: 255-258.

21. Kohlmeier, L., K.G. Weterings, S. Steck and F.J. Kok, 1997. Tea and cancer prevention: An evaluation of the epidemiologic literature. Nutr. Cancer, 27: 1-13.
22. Zhang, X., B. Zhang, X. Li, X. Wang and H. Nakama, 2000. Relative risk of dietary components and colorectal cancer. European J. Med. Res., 5: 451-454.
23. Zhang, B., X. Li, H. Nakama, X. Zhang, N. Wei and L. Zhang, 2002. A case-control study on risk of changing food consumption for colorectal cancer. Cancer Investigation, 20: 458-463.
24. Imai, K., K. Suga and K. Kanachi, 1997. Cancer preventive effects of drinking green tea amonst a Japanese population. Prevention Medicine, 26: 769-775.
25. Plummer, S.M., K.A. Holloway, M.M. Manson, R.J. Munks, A. Kaptein, S. Farrow and L. Howells, 1999. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. Oncogene, 18: 6013-6020.
26. Garcea, G., D.J. Jones, R. Singh, A. Dennison, P.B. Farmer, R.A. Sharma, W.P. Steward, A. Gescher and D.P. Berry, 2004. Detection of curcumin and its metabolites in hepatic and portal blood of patients following oral administration. Br. J. Cancer, 90: 1011-1015.
27. Sharma, R.A., C.R. Ireson, R.D. Verschoyle, K.A. Hill, M.L. Williams, C. Leuratti, M.M. Manson, L.J. Marnett, W.P. Steward and A. Gescher, 2001. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: Relationship with drug levels. Clinical Cancer Res., 7: 1452-1458.
28. Mahmoud, N.N., A.M. Carothers, D. Grunberger, R.T. Bilinski, M.R. Churchill, C. Martucci, H.L. Newmark and M.M. Bertagnolli, 2000. Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis. Carcinogenesis, 21: 921-927.
29. Mori, H., K. Niwa, Q. Zheng, Y. Yamada, K. Sakata and N. Yoshimi, 2001. Cell proliferation in cancer prevention; effects of preventive agents on estrogen-related endometrial carcinogenesis model and on an in vitro model in human colorectal cells. Mutation Res., pp: 480-481, 201-207.
30. Samaha, H.S., G.J. Kelloff, V. Steele, C.V. Rao and B.S. Reddy, 1997. Modulation of apoptosis by sulindac, curcumin, phenylethyl-3-methylcaffeate and 6-phenylhexyl isothiocyanate: Apoptotic index as a biomarker in colon cancer chemoprevention and promotion. Cancer Res., 57: 1301-1305.
31. Hirose, M., S. Takahashi, K. Ogawa, M. Futakuchi and T. Shirai, 1999. Phenolics: Blocking agents for heterocyclic amine-induced carcinogenesis. Food Chem. Toxicolol., 37: 985-992.
32. Churchill, M., A. Chadburn, R.T. Bilinski and M.M. Bertagnolli, 2000. Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile. J. Surgical Res., 89: 169-175.
33. Wolter, F. and J. Stein, 2002. Resveratrol enhances the differentiation induced by butyrate in caco-2 colon cancer cells. J. Nutr., 132: 2082-2086.
34. Delmas, D., P. Passilly-Degrace, B. Jannin, M.C. Malki and N. Latruffe, 2002. Resveratrol, a chemopreventive agent, disrupts the cell cycle control of human SW480 colorectal tumor cells. Intl. J. Mol. Medicine, 10: 193-199.
35. Schneider, Y., F. Vincent, B. Duranton, L. Badolo, F. Gosse, C. Bergmann, N. Seiler and F. Raul, 2000. Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. Cancer Lett., 158: 85-91.
36. Liang, Y.C., S.H. Tsai, L. Chen, S.Y. Lin-Shiau and J.K. Lin, 2003. Resveratrol-induced G2 arrest through the inhibition of CDK7 and p34CDC2 kinases in colon carcinoma HT29 cells. Biochem. Pharmacol., 65: 1053-1060.
37. Wolter, F., B. Akoglu, A. Clausnitzer and J. Stein, 2001. Down regulation of the cyclin D1/Cdk4 complex occurs during resveratrol- induced cell cycle arrest in colon cancer cell lines. J. Nutr., 131: 2197-2203.
38. Mahyar-Roemer, M., A. Katsen, P. Mestres and K. Roemer, 2001. Resveratrol induces colon tumor cell apoptosis independently of p53 and precede by epithelial differentiation, mitochondrial proliferation and membrane potential collapse. Intl. J. Cancer, 94: 615-622.
39. Mahyar-Roemer, M., H. Kohler and K. Roemer, 2002. Role of Bax in resveratrol-induced apoptosis of colorectal carcinoma cells. BMC Cancer, 2: 27.
40. Uesato, S., Y. Kitagawa, M. Kamishimoto, A. Kumagai, H. Hori and H. Nagasawa, 2001. Inhibition of green tea catechins against the growth of cancerous human colon and hepatic epithelial cells. Cancer Lett., 170: 41-44.
41. Salucci, M., L.A. Stivala, G. Maiani, R. Bugianesi and V. Vannini, 2002. Flavonoids uptake and their effect on cell cycle of human colon adenocarcinoma cells Caco2. Br. J. Cancer, 86: 1645-1651.
42. Lambert, J. and C. Yang, 2003. Cancer chemopreventive activity and bioavailability of tea and tea polyphenols. Mutation Res., 9474: 1-8.

43. Chen, Z.P., J.B. Schell, C.T. Ho and K.Y. Chen, 1998. Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett., 129: 173-179.
44. Xu, M., A.C. Bailey, J.F. Hernaez, C.R. Taoka, H.A. Schut and R.H. Dashwood, 1996. Protection by green tea, black tea and indole-3-carbinol against 2-amino-3-methylimidazo[4,5-f]quinoline-induced DNA adducts and colonic aberrant crypts in the F344 rat. Carcinogenesis, 17: 1429-1434.
45. Kan, H., M. Onda, N. Tanaka and K. Furukawa, 1996. [Effect of green tea polyphenol fraction on 1,2-dimethylhydrazine DMH- induced colorectal carcinogenesis in the rat]. Nippon Ika Daigaku Zasshi, 63: 106-116.
46. Dashwood, R.H., M. Xu, J.F. Hernaez, N. Hasaniya, K. Youn and A. Razzuk, 1999. Cancer chemopreventive mechanisms of tea against heterocyclic amine mutagens from cooked meat. Proceedings Society Experimnental Bioliogical Medicine, 220: 239-243.
47. Berger, S., S. Gupta, C. Belfi, D. Gosky and H. Mukhtar, 2001. Green tea constituent-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells. Biochem. Biophysical Res. Communicat., 288: 101-105.
48. Santana-Rios, G., G.A. Orner, M. Xu, M. Izquierdo-Pulido and R.H. Dashwood, 2001. Inhibition by white tea of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced colonic aberrant crypts in the F344 rat. Nutrition and Cancer, 41: 98-103.
49. van de Wetering, M., E. Sancho and C. Veweij, 2002. The beta-catenin/TCF4 complex imposes a crypt prgenitor phenotype on colorectal cancer cells. Cell, 111: 241-250.
50. Chun, K.S., S.H. Kim, Y.S. Song and Y.J. Surh, 2004. Celecoxib inhibits phorbol ester-induced expression of COX-2 and activation of AP-1 and p38 MAP kinase in mouse skin. Carcinogenesis, 25: 13-22.
51. Shishodia, S., D. Koul and B.B. Aggarwal, 2004. Cyclooxygenase COX-2 inhibitor celecoxib abrogates TNF-induced NF-kappa B activation through inhibition of activation of I kappa B alpha kinase and Akt in human non-small cell lung carcinoma: Correlation with suppression of COX-2 synthesis. J. Immunol., 173: 2011-22.
52. Schneider, Y., B. Duranton, F. Gosse, R. Schleiffer, N. Seiler and F. Raul, 2001. Resveratrol inhibits intestinal tumorigenesis and modulates host-defense-related gene expression in an animal model of human familial adenomatous polyposis. Nutr. Cancer, 39: 102-107.
53. Hansen-Petrik, M.B., M.F. McEntee, B. Jull, H. Shi, M.B. Zemel and J. Whelan, 2002. Prostaglandin E-2 protects intestinal tumors from nonsteroidal anti-inflammatory drug-induced regression in ApcMin/+ mice. Cancer Res., 62: 403-408.
54. Jacoby, R.F., D.J. Marshall, M. Newton, K. Tutsch, C.E. Cole, R.A. Lubet, G.J. Kelloff, A. Verma, A.R. Moser and W.F. Dove, 1996. Chemoprevention of spontaneous intestinal adenomas in the Apc mutant Min mouse model by the nonsteroidal anti-inflammatory drug piroxicam. Gastroenterology, 110: A535-A535.
55. Jacoby, R.F., K. Seibert, K., C.E. Cole, G. Kelloff and R.A. Lubet, 2000. The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the min mouse model of adenomatous polyposis. Cancer Res., 60: 5040-5044.
56. Jacoby, R.F., C.E. Cole, K. Tutsch, M.A. Newton, G. Kelloff, E.T. Hawk and R.A. Lubet, 2000. Chemopreventive efficacy of combined piroxicam and difluoromethylornithine treatment of Apc mutant Min mouse adenomas and selective toxicity against Apc mutant embryos. Cancer Res., 60: 1864-1870.
57. Jacoby, R.F., C.E. Cole, E.T. Hawk and R.A. Lubet, 2002. Ursodeoxycholate plus low dose sulindac is an effective and well tolerated chemopreventive agent combination in the Min mouse model of adenomatous polyposis. Gastroenterology, 122: M914.
58. Boolbol, S.K., A.J. Dannenberg, A. Chadburn, C. Martucci, X.J. Guo, J.T. Ramonetti, M. Abreu-Goris, H.L. Newmark, M.L. Lipkin, J.J. DeCosse and M.M. Bertagnolli, 1996. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. Cancer Res., 56: 2556-2560.
59. Chiu, C.H., M. McEntee and J. Whelan, 1997. Eicosanoid biosynthesis is not correlated with tumor load in the Min/+ mouse model. Faseb J., 11: 3333-3333.
60. Ritland, S.R. and S.J. Gendler, 1999. Chemoprevention of intestinal adenomas in the ApcMin mouse by piroxicam: kinetics, strain effects and resistance to chemosuppression. Carcinogenesis, 20: 51-58.
61. Suganuma, M., Y. Ohkura, S. Okabe and H. Fujiki, 2001. Combination cancer chemoprevention with green tea extract and sulindac shown in intestinal tumor formation in min mice. J. Cancer Res., Clinical Oncol., 127: 69-72.

62. Torrance, C.J., P.E. Jackson, E. Montgomery, K.W. Kinzler, B. Vogelstein, A. Wissner, M. Nunes, P. Frost and C.M. Discafani, 2000. Combinatorial chemoprevention of intestinal neoplasia. Nature Medicine, 6: 1024-1028.
63. Metz, N., A. Lobstein, Y. Schneider, F. Gosse, R. Schleiffer, R. Anton and F. Raul, 2000. Suppression of azoxymethane-induced preneoplastic lesions and inhibition of cyclooxygenase-2 activity in the colonic mucosa of rats drinking a crude green tea extract. Nutrition and Cancer, 38: 60-64.
64. Rao, C.V., B. Simi and B.S. Reddy, 1993. Inhibition by dietary curcumin of azoxymethane-induced ornithine decarboxylase, tyrosine protein kinase, arachidonic acid metabolism and aberrant crypt foci formation in the rat colon. Carcinogenesis, 14: 2219-2225.
65. Rao, C.V., T. Kawamori, R. Hamid and B.S. Reddy, 1999. Chemoprevention of colonic aberrant crypt foci by an inducible nitric oxide synthase-selective inhibitor. Carcinogenesis, 20: 641-644.
66. Steele, V.E., D. Bagheri, D.A. Balentine, C.W. Boone, R. Mehta, M.A. Morse, S. Sharma, C.C. Sigman, G.D. Stoner, M.J. Wargovich, J.H. Weisburger, S. Zhu and G.J. Kelloff, 1999. Preclinical efficacy studies of green and black tea extracts. Proc. Soc. Exptl. Biol. Medicine, 220: 210-212.
67. Kwon, Y., J. Montgomery, M. Malik and B. Magnuson, 2002. Ageing alters the inhibition of colonic aberrant crupt foci by curcumin. J. Nutr., 132: 3541S.
68. Jia, X. and C. Han, 2001. Effects of green tea on colonic aberrant crypt foci and proliferative indexes in rats. Nutr. Cancer, 39: 239-243.
69. Rang, H.P., M.M. Dale and J.M. Ritter, 1998. Pharmacology. Churchill Livingstone.
70. Mulder, T.P., C.J. van Platerink, P.J. Wijnana Schyl and J.M. van Amelsvoort, 2001. Analysis of theaflavins in biological fluids using liquid chrmoatrography-electrospray mass spectrometry. J. Chromatrophy B Biomedical Scientic Applications, 760: 271.
71. Ireson, C.R., D.J. Jones, S. Orr, M.W. Coughtrie, D.J. Boocock, M.L. Williams, P.B. Farmer, W.P. Steward and A.J. Gescher, 2002. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiology Biomarkers and Prevention, 11: 105-111.
72. Sharma, R.A., H.R. McLelland, K.A. Hill, C.R. Ireson, S.A. Euden, M.M. Manson, M. Pirmohamed, L.J. Marnett, A.J. Gescher and W.P. Steward, 2001 Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clinical Cancer Res., 7: 1894-1900.
73. Perkins, S., R.D. Verschoyle, K. Hill, I. Parveen, M.D. Threadgill, R.A. Sharma, M.L. Williams, W.P. Steward and A.J. Gescher, 2002. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiology Biomarkers and Prevention, 11: 535-540.
74. Asensi, M., I. Medina, I., A. Ortega, J. Carretero, M.C. Bano, E. Obrador and J.M. Estrela, 2002. Inhibition of cancer growth by resveratrol is related to its low bioavailability. Free Radical Biology and Medicine, 33: 387-398.
75. Marier, J.F., P. Vachon, A. Gritsas, J. Zhang, J.P. Moreau and M.P. Ducharme, 2002. Metabolism and disposition of resveratrol in rats: Extent of absorption, glucuronidation and enterohepatic recirculation evidenced by a linked-rat model. J. Pharmacol. Exptl. Therapeutics, 302: 369-373.
76. Yu, C.W., Y.G. Shin, A. Chow, Y.M. Li, J.W. Kosmeder, Y.S. Lee, W.H. Hirschelman, J.M. Pezzuto, R.G. Mehta and R.B. van Breemen, 2002. Human, rat and mouse metabolism of resveratrol. Pharmaceutical Res., 19: 1907-1914.
77. Kuhnau, J., 1976. The flavonoids. A class of semi-essential food components: Their role in human nutrition. World Review of Nutrition and Diet, 24: 117-119.
78. Kuhnle, G., J. Spencer, G. Chowrimootoo, H. Schoreter, E. Debnam, K. Srai, C. Rice-Evans and U. Hahn, 2000. Resveratrol is absrobed in the samll intestine as resveratrol glucuronide. Biochem. Biophysical Res. Communicat., 272: 212-217.
79. Azuma, K., K. Ippoushi, H. Ito, H. Higashio and J. Terao, 2002. Combination of lipids and emulsifiers enhances the absorption of orally administered quercetin in rats. J. Agril. Food Chem., 50: 1706-1712.
80. Shoba, G., D. Joy, T. Joseph, M. Majeed, R. Rajendran and P.S. Srinivas, 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Medicine, 64: 353-356.
81. Chen, L., L. Mao-Jung, H. Li and C. Yang, 1997. Absorption, distribution and elimination of tea polyphenols in rats. Drug Metabolism and Disposition, 25: 1045-1050.
82. Hagerman, A., K. Riedl and G. Jones, 1998. High molecular weight plant polyphenols tannins as biological anti-oxidants. J. Agril. Food Chem., 46: 1887-1892.
83. Bravo, L., R. Abia, M.A. Eastwood and F. Saura-Calixto, 1994. Degradation of polyphenols catechin and tannic acid in the rat intestinal tract. Effect on colonic fermentation and faecal output. Br. J. Nutr., 71: 933-946.

84. Cheng, A.L., C.H. Hsu, J.K. Lin, M.M. Hsu, Y.F. Ho, T.S. Shen, J.Y. Ko, J.T. Lin, B.R. Lin, W. Ming-Shiang, H.S. Yu, S.H. Jee, G.S. Chen, T.M. Chen, C.A. Chen, M.K. Lai, Y.S. Pu, M.H. Pan, Y.J. Wang, C.C. Tsai and C.Y. Hsieh, 2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res., 21: 2895-2900.
85. Ireson, C.R., D.J.L. Jones, S. Orr, M.W.H. Coughtrie, D.J. Boocock, M.L. Williams, P.B. Farmer, W.P. Steward and A.L. Gescher, 2002. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol. Biomarkers and Prevention, 11: 105-111.
86. Kunchandy, E. and M.N. Rao, 1990. Oxygen radical scavenging activity of curcumin. Indian J. Pharmaceuticals, 87: 79-87.
87. Huang, M.T., T. Lysz, T. Ferraro, T.F. Abidi, J.D. Laskin and A.H. Conney, 1991. Inhibitory effects of curcumin on *in vitro* lipoxygenase and cyclooxygenase activities in mouse epidermis. Cancer Res., 51: 813-819.
88. Reddy, A.C. and B.R. Lokesh, 1992. Studies on spice principles as antioxidants in the inhibition of lipid peroxidation of rat liver microsomes. Molecular Cell Biochem., 111: 117-124.
89. Sharma, O.P., 1976. Antioxidant activity of curcumin and related compounds. Biochem. Pharmacol., 25: 1811-1812.
90. Subramanian, M., Sreejayan, M.N. Rao, T.P. Devasagayam and B.B. Singh, 1994. Diminution of singlet oxygen-induced DNA damage by curcumin and related antioxidants. Mutation Res., 311: 249-255.
91. August, D.A., J. Landau, D. Caputo, J. Hong, M.J. Lee and C.S. Yang, 1999. Ingestion of green tea rapidly decreases prostaglandin E2 levels in rectal mucosa in humans. Cancer Epidemiology, Biomarkers and Prevention., 8, 709-713.
92. Pisters, K., R. Newman, B. Coldman, D. Shin, F. Khuri, W. Hong, B. Glisson and J. Lee, 2001. Phase I trial of oral green tea extract in adult patients with solid tumors. J. Clinical Oncol., 19: 1830-1838.
93. Chung, F.L., J. Schwartz, C.R. Herzog and Y.M. Yang, 2003. Tea and cancer prevention: Studies in animals and humans. J. Nutr., 133: 3268S-3274S.
94. Huerta, S., R.W. Irwin, D. Heber, V.L. Go, H.P. Koeffler, M.R. Uskokovic and D.M. Harris, 2002. 1 alpha, 25-OH2-D3 and its synthetic analogue decrease tumor load in the Apcmin Mouse. Cancer Res., 62: 741-746.
95. Collett, G.P., C.N. Robson, J.C. Mathers and F.C. Campbell, 2001. Curcumin modifies Apcmin apoptosis resistance and inhibits 2-amino 1-methyl-6-phenylimidazo[4, 5-b]pyridine PhIP induced tumour formation in Apcmin mice. Carcinogenesis, 22: 821-825.
96. Pereira, M.A., L.H. Barnes, V.L. Rassman, G. Kelloff and V. Steele, 1994. Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. Carcinogenesis, 15: 1049-1054.
97. Morishita, Y., N. Yoshimi, K. Kawabata, K. Matsunaga, S. Sugie, T. Tanaka and H. Mori, 1997. Regressive effects of various chemopreventive agents on azoxymethane-induced aberrant crypt foci in the rat colon. Japanese J. Cancer Res., 88: 815-820.
98. Wargovich, M.J., A. Jimenez, K. McKee, V. Steele, M. Velasco, J. Woods, R. Price, K. Gray and G. Kelloff, 2000. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. Carcinogenesis, 21: 1149-1155.
99. Wargovich, M.J., C.D. Chen, A. Jimenez, V.E. Steele, M. Velasco, L.C. Stephens, R. Price, K. Gray and G.J. Kelloff, 1996. Aberrant crypts as a biomarker for colon cancer: Evaluation of potential chemopreventive agents in the rat. Cancer Epidemiol. Biomarkers and Prevention, 5: 355-360.
100. Rao, C.V., H.L. Newmark and B.S. Reddy, 1998. Chemopreventive effect of squalene on colon cancer. Carcinogenesis, 19: 287-290.
101. Reddy, B.S., C.V. Rao and K. Seibert, 1996. Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. Cancer Res., 56: 4566-4569.
102. Pereira, M.A., L.H. Barnes, V.L. Rassman, G.V. Kelloff and V.E. Steele, 1994. Use of azoxymethane-induced foci of aberrant crypts in rat colon to identify potential cancer chemopreventive agents. Carcinogenesis, 15: 1049-1054.
103. Charalambous, D., C. Farmer and P.E. O'Brien, 1996. Sulindac and indomethacin inhibit formation of aberrant crypt foci in the colons of dimethyl hydrazine treated rats. J. Gastroenterol. Hepatol., 11: 88-92.
104. Rao, C.V., I. Cooma, M.V. Swamy, B. Simi and B.S. Reddy, 2001. Modulation of inductible nitric oxide synthase ans cyclooxygenase activities by curcumin during different stages of experimental colon carcinogenesis. Proceedings of the American Association for Cancer Res., 42: 3084.

105. Tessitore, L., A. Davit, I. Sarotto and G. Caderni, 2000. Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21CIP expression. Carcinogenesis, 21: 1619-1622.
106. Rao, A.V., K. Tokumo, J. Rigotty, E. Zang, G. Kelloff and B.S. Reddy, 1991. Chemoprevention of colon carcinogenesis by dietary administration of piroxicam, alpha-difluoromethylornithine, 16 alpha-fluoro-5-androsten-17-one and ellagic acid individually and in combination. Cancer Res., 51: 4528-4534.
107. Reddy, B.S., K. Tokumo, N. Kulkarni, C. Aligia and G. Kelloff, 1992. Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. Carcinogenesis, 13: 1019-1023.
108. Li, H., P.M. Kramer, R. Lubet, V. Steele, G. Kelloff and M.A. Pereira, 1999. Termination of piroxicam treatment and the occurrence of azoxymethane-induced colon cancer in rats. Cancer Lett., 147: 187-193.
109. Rao, C.V., A. Rivenson, B. Simi, E. Zang, G. Kelloff, V. Steele and B.S. Reddy, 1995. Chemoprevention of colon carcinogenesis by sulindac, a nonsteroidal anti-inflammatory agent. Cancer Res., 55: 1464-1472.
110. Reddy, B.S., Y. Hirose, R. Lubet, V. Steele, G. Kelloff, S. Paulson, K. Seibert and C.V. Rao, 2000. Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib, administered during different stages of carcinogenesis. Cancer Res., 60: 293-297.
111. Kawamori, T., C.V. Rao, K. Seibert and B.S. Reddy, 1998. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis. Cancer Res., 58: 409-412.
112. Huang, M.T., Y.R. Lou, W. Ma, H.L. Newmark, K.R. Reuhl and A.H. Conney, 1994. Inhibitory effects of dietary curcumin on forestomach, duodenal and colon carcinogenesis in mice. Cancer Res., 54: 5841-5847.
113. Kawamori, T., R. Lubet, V.E. Steele, G.J. Kelloff, R.B. Kaskey, C.V. Rao and B.S. Reddy, 1999. Chemopreventive effect of curcumin, a naturally occurring anti- inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res., 59: 597-601.
114. Rao, C.V., A. Rivenson, B. Simi and B.S. Reddy, 1995. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res., 55: 259-266.
115. Yamane, T., N. Hagiwara, M. Tateishi, S. Akachi, M. Kim, J. Okuzumi, Y. Kitao, M. Inagake, K. Kuwata and T. Takahashi, 1991. Inhibition of azoxymethane-induced colon carcinogenesis in rat by green tea polyphenol fraction. Japanese J. Cancer Res., 82: 1336-1339.