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A Lifestyle/Nutraceutical Program for Minimizing Colorectal Cancer Risk by Opposing β-Catenin Activity in Colonic Epithelium

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Abstract

Up-regulated activity of β-catenin, which serves as a coactivator for TCF/LEF transcription factors and thereby promotes transcription of genes promoted cellular proliferation, opposing apoptosis, and aiding cellular migration, is known to be a key driver of colorectal cancer induction. An analysis of the molecular pathways influencing β-catenin activation indicates that lifestyle, pharmaceutical, and nutraceutical measures linked in epidemiology and rodent studies to decreased risk for this malignancy, are protective at least in part owing to a down-regulatory impact on β-catenin activity. Such measures include whole-food fiber-rich plant-based diets, ingestion of cruciferous vegetables, aerobic exercise training, daily low-dose aspirin, metformin therapy, and increased intake of vitamin D, calcium, and soy isoflavones. There is also reason to suspect that supplementation with high doses of folate and of biotin may oppose β-catenin activity and colorectal cancer induction via increased production of cGMP in colorectal epithelium, that the sesame lignin sesamol may likewise provide protection in this regard by targeting colonic NOX1 activity, that quercetin or more soluble derivatives thereof may decrease colorectal cancer risk via inhibition of the kinase CK2, and that astaxanthin may decrease this risk by increasing plasma adiponectin and via antioxidant activity. Scope for prevention of colorectal cancer – still the number 2 cancer killer despite screening strategies that can often detect it in a surgically curable stage – may be quite substantial.

Keywords: Colorectal cancer prevention; Beta-catenin; Aspirin; Metformin; Vitamin D; Calcium; Isoflavonees, Folate, Biotin, Sesamol; Quercetin; Astaxanthin

Targeting β-Catenin for Prevention of Colorectal Cancer

Despite the availability of clinical strategies that are reasonably effective for detecting it in a surgically curable stage, colorectal cancer remains the number 2 cause of cancer mortality in the Western world. A great deal of evidence indicates that the pro-proliferative, anti-apoptotic effects of excessive, uncontrolled beta-catenin activity play a key role in the induction and progression of a large majority of colorectal cancers [1,2]. The thesis of this essay is that factors known to either promote or oppose the induction of colorectal cancer do so in large part via modulation of beta-catenin activity – and that a lifestyle/nutraceutical regimen designed to oppose this activity may have considerable potential for colorectal cancer prevention.

Beta-catenin acts as a coactivator for the T-cell factor/lymphoid enhancer factor (TCF/LEF) class of transcription factors [3,4]. When nuclear levels of β-catenin are low, the corepressor groucho protein binds to TCF, such that TCF functions as a repressor of genes whose promoter it binds to. But when nuclear levels of β-catenin rise, the latter displaces groucho in binding to TCF, and TCF then promotes the transcription of these genes. The genes whose transcription is promoted by the TCF/β-catenin complex code for a number of proteins that promote cell proliferation, inhibit apoptosis, and degrade the extracellular matrix - proteins that promote cancerous transformation and metastatic behavior. These include c-myc, cyclin D1, survivin, and metalloproteinase-7 [1,5].

Mechanisms that Modulate β-Catenin's Expression, Localization, and Coactivational Activity

In the absence of certain activating signals, most of the β-catenin in the cell binds to cadherins at the plasma membrane surface [6,7]. And much of the cytoplasmic β-catenin is tied up in a so-called "Destruction complex" which includes the proteins axin,

adenomatous polyposis coli (APC), casein kinase-1a (CK-1a), and glycogen synthase kinase-3β (GSK-3β) [8]. After a "priming" phosphorylation of β-catenin by CK-1a on Ser45, GSK-3β then can phosphorylate it on Ser33, Ser37, and Thr41, which prepares it for ubiquitinylation and subsequent proteasomal degradation. These joint mechanisms cooperate to minimize nuclear β-catenin. In a very high proportion of colorectal cancers, loss-of-function mutations of APC preclude the formation of the destruction complex, such that ubiquitination-dependent proteasomal disposal of β-catenin is greatly compromised [9]. APC(Min/+) mice, which are heterozygous for loss of APC function, are highly prone to development of intestinal cancer, and are widely employed as a model of colorectal cancer induction [10].

Activated Akt can confer an inhibitory phosphorylation on GSK-3β, such that its ability to phosphorylate and prime for degradation β-catenin is suppressed; moreover, Akt can phosphorylate β-catenin at Ser552, which aids β-catenin's translocation to the nucleus [11,12]. And β-catenin can be phosphorylated at both Ser552 and Ser675 by protein kinase A (PKA), the kinase activated by cAMP; these modifications stabilize β-catenin, promote its translocation to the nucleus, and enhance its interaction with TCF [13]. Hence, both Akt and PKA unleash β-catenin's ability to promote gene transcription.

In addition, certain tyrosine kinases such as c-Src can phosphorylate β-catenin at Tyr654, which blocks its ability to bind to E-cadherin [14]. This modification also promotes nuclear translocation of β-catenin, as well as its ability to act as a co-activator for TCF [15,16].

Whereas cAMP, via PKA, acts to boost β-catenin's activity, cGMP, acting via protein kinase G (PKG), has the opposite effect. PKG has been shown to lower cellular β-catenin levels and decrease its mRNA expression – possibly owing to suppressed transcription of the β-catenin gene CTNNB1 [17-21]. The mechanism whereby PKG achieves this still requires clarification. PKG can also decrease the nuclear interaction of β-catenin with TCF by boosting intra-nuclear levels of FOXO4, which competes with TCF for binding to β-catenin as a coactivator [22]. Colon epithelium expresses a guanylate cyclase 2C membrane receptor which generates cGMP in response to paracrine stimulation by the hormones guanylin and uroguanylin; this system is known to act as a tumor suppressor, and it tends to be lost or down-regulated during the process of colon carcinogenesis [23].

Physiologically important modulation of β-catenin activity is also mediated by estrogen receptor-β (ERβ), AMP-activated kinase (AMPK), and the kinase CK2 (formerly known as casein kinase-2). When activated via a ligand, ERβ migrates to the nucleus and suppresses β-catenin expression at the mRNA level; whether it binds to the CTNNB1 promoter has not been established [24]. AMPK likewise down-regulates β-catenin expression in colorectal epithelium; this is associated with a failure of Akt to confer an activating/stabilizing phosphorylation on Ser552 [25]. Recent studies suggest that this reflects AMPK-mediated inhibition of PI3K/Akt activity, and/or a direct binding of AMPK to β-catenin that may impede its interaction with Akt [25,26]. CK2, which is ubiquitously expressed, and over-expressed in colorectal cancer, promotes β-catenin stability and enhances its ability to enable TCF/LDF-mediated transcription [27-30]. CK2 confers a phosphorylation on Akt which appears necessary for the latter's ability to phosphorylate and stabilize β-catenin [31,32].

As we will now see, this simple overview now prepares us to understand a range of practical strategies for suppressing colorectal cancer induction. These mechanisms are depicted in Figure 1.

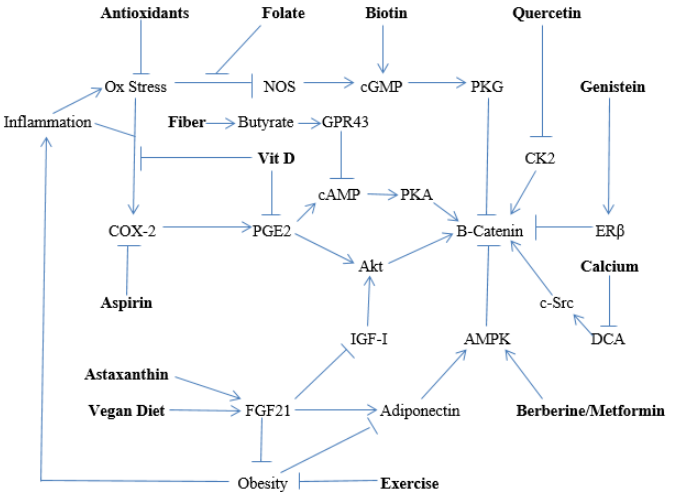

Figure 1: Suppression of beta-catenin activity for prevention of colorectal CA.

Protective factors are high-lighted in bold.

Opposing Cox-2 Activity - Aspirin, Vitamin D, Antioxidants, and Fiber

Expression of cyclooxygenase-2 (COX-2) is elevated in about 85% of colorectal cancers, and about half of adenomas [33]. Constitutive COX-1 and inducible COX-2 are expressed in normal colorectal epithelium, and their joint expression is elevated in the normal colonic mucosa of patients who have previously developed colorectal cancer [34]. A key product of COX activity, prostaglandin E2 (PGE2), acts in an autocrine/paracrine fashion on colorectal epithelium via EP2 receptors to promote generation of cAMP via adenylate cyclase, and via EP4 receptors to stimulate PI3K/Akt activity [35]. Hence, PGE2 acts via both cAMP and Akt to boost β-catenin activity. (Conversely, beta catenin activity promotes transcription of the COX-2 gene [36].) This likely explains why regular use of NSAID drugs has been linked to lower risk for colorectal cancer [37,38]. In this regard, daily low-dose

aspirin, which is relatively safe for use as a preventive strategy, has been found to notably lower risk for this cancer in a meta-analysis of large-scale lengthy randomized controlled trials; risk was about 25% lower in those who had taken daily low-dose aspirin for at least 5 years [39].

Colorectal epithelium expresses the 25-hydroxyvitamin D 1-alpha-hydroxylase (CYP27B1) activity required for conversion of circulating 25-hydroxyvitamin D to the active hormone calcitriol; it also expresses vitamin D receptors [40]. Hence, vitamin D's hormonal activity within colorectal epithelium tends to vary directly with plasma levels of 25-hydroxyvitamin D. Notably, in a range of tissues, calcitriol has been shown to boost mRNA and protein expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the chief enzyme that catabolizes PGE2 to an inactive form [41,42]. Moreover, there is also evidence that vitamin D activity can suppress cox-2 expression, possibly because it induces expression of MAP kinase phosphatase-1, an antagonist of MAP kinase activities that activate the promoter of the COX2 gene [43-46]. Consistent with this analysis, vitamin D supplementation was shown to markedly lower the ratio of COX-2/15-PGDH expression in the rectal mucosa of colorectal adenoma patients [47]. Notably, a meta-analysis of 15 case-control or cohort studies has found that risk for colorectal cancer is about one-third lower in the upper quantile as opposed to the lower quantile of plasma 25-hydroxyvitamin D [48].

Colitis notably increases risk for colorectal cancer, and oxidative stress both characterizes and promotes inflammation. Indeed, oxidative stress is likely to play a role in cox-2 induction during colorectal carcinogenesis, as it tends to boost the MAP kinase and NF-kappaB activities that drive cox-2 expression at the transcriptional level [49]. Colonic epithelium expresses the NOX1 isoform of NADPH oxidase [50,51]. Inhibition of NOX1 activity in a human colon cancer-derived cell line via apocynin, siRNA transfection, or the sesame lignin sesamol - which suppresses NOX1 mRNA expression in these cells - decreases COX-2 expression at the transcriptional level [52]. Moreover, dietary administration of sesamol suppresses intestinal polyp formation in APC(Min/+) mice. If this lignin were to become available as a nutraceutical, it might have potential as a chemopreventive agents for colorectal cancer.

The unconjugated bilirubin evolved by heme oxygenase activity functions as an inhibitor of certain NAPDH oxidase complexes, and its activity in this regard is mimicked by the phycocyanobilin chromophore richly supplied by certain cyanobacteria and blue-green algae - most notably spirulina, traditionally employed as a food in some cultures and now used as a nutraceutical [53-57]. However, the only study to evaluate bilirubin's impact on NOX1 activity failed to demonstrate inhibition - whereas the carbon monoxide evolved by heme oxygenase activity was inhibitory [58]. Nonetheless, oral administration of phycocyanin, the algal protein to which phycocyanobilin is covalently attached, has been shown to suppress colon carcinogenesis in dimethylhydrazine-treated mice [59,60]. Perhaps this reflects its impact on NOX2-dependent NADPH oxidase activity in pro-inflammatory myeloid cells in the intestinal mucosa.

Phase 2 inducers, such as the sulforaphane provided by cruciferous vegetable, promote expression of a range of antioxidant enzymes via activation of the nrf2 transcription factor, and are thought to have important potential for colorectal cancer prevention [61]. In particular, they induce expression of heme oxygenase-1, which can inhibit NOX1 via generated carbon monoxide [58,62]. In APC(Min/+) mice that are further genetically modified to lack nrf2 expression, intestinal expression of cox-2 is enhanced, and intestinal tumorigenesis is notably up-regulated; conversely, administration of phase 2 inducers suppresses intestinal carcinogenesis in APC(Min/+) mice and mice treated with azoxymethane/dextran sodium sulfate [63-65]. These findings correlate nicely with epidemiological studies linking high intakes of cruciferous vegetables to decreased risk for colorectal cancer - as ratified in a meta-analysis [65,66]. The nutraceutical phase 2 inducer lipoic acid might likewise have protective potential in this regard [67-69] albeit its impact on colorectal cancer induction in rodents has so far received little if any investigation.

The carotenoid antioxidant astaxanthin - more effective than vitamin E for preventing membrane oxidation - shows protective effects in rodent models of colorectal cancer induction induced by dimethylhydrazine, azoxymethane, and dextran sodium sulfate; one of these studies reports suppression of COX-2 induction [70-73]. These studies suggest that astaxanthin may have potential for prevention of inflammation-linked colorectal carcinogenesis.

Elevated Western risk of colorectal cancer - as compared to the much lower rates seen in the rural Third World - have suggested that low-fat, high fiber diets may confer protection from this cancer [74]. Curiously, prospective epidemiology has failed to establish a role for dietary fat in this regard, but high fiber diets do emerge as protective in prospective and case-control studies [75-77]. Diets rich in soluble fiber and/or "Resistant" carbohydrate provide substrate for the production of short-chain fatty acids such as butyrate by colonic bacteria [78]. These short-chain fatty acids serve as metabolic fuel for the colon epithelium, but they also activate the free fatty acid receptor 2 (FFAR2 - a.k.a GPR43) receptor expressed by these epithelial cells. Genetic knockout of this receptor boosts intestinal tumor yields in APC(Min/+) mice and in mice treated with the colon carcinogen azoxymethane [79]. Notably, FFAR2 is a seven-pass receptor capable of activating $G\alpha_i$, which suppresses adenylate cyclase activation and hence lowers cellular levels of cAMP [80]. Hence, FFAR2 acts as a functional

antagonist of the cancer-promoting activity of cox-2/PGE2.

Stimulating AMPK with Metformin, Berberine, and Vegan Diet

The ability of AMPK to decrease β-catenin activity helps to explain epidemiology pointing to lower risk for colorectal cancer in diabetics who use metformin as opposed to other antidiabetic medications [81-84]. The nutraceutical berberine, which like berberine can activate AMPK, and is widely used for management of type 2 diabetes in China, also appears to have potential for prevention of colorectal cancer [85-87]. Indeed, berberine reduces tumorigenesis in APC(Min/+) mice, and was shown to decrease risk for recurrence of colorectal adenoma in a multi-center double-blind randomized controlled study [88,89].

The adipocyte-derived hormone adiponectin boosts AMPK activity in its target tissues - which include colonic epithelium; moreover, adiponectin knockout boosts colorectal carcinogenesis in fat-fed and in APC(Min/+) mice [90-92]. Obesity, most notably abdominal obesity, is associated with a markedly increased risk for colorectal cancer - as well as low plasma levels of adiponectin [93,94]. Epidemiological studies have concluded that low adiponectin levels are likely to play a mediating role in obesity's impact on colorectal cancer risk (in contrast to the adipokine leptin) [95].

Whereas weight loss can boost adiponectin levels, adipocyte production of this factor is also boosted by fibroblast growth factor 21 (FGF21); indeed, increased adiponectin production appears to explain the favorable impact of FGF21 on insulin resistance and glycemic control in mice [96,97]. Hepatic production and plasma levels of FGF21 are boosted by dietary restriction of protein or of certain essential amino acids - a feature of low-protein plant-based (vegan) diets; indeed, a recent clinical study found that plasma FGF21 levels are about three-fold higher in vegans than in omnivores [98-100]. Hence, the increased FGF21 activity associated with vegan diets may act to lower colorectal cancer risk both by a rapid impact on adiponectin production, and by a longer term tendency to prevent or reverse obesity [98]. The ability of a low-protein diet to enhance plasma levels of adiponectin has been demonstrated in rats [101].

Although astaxanthin is typically thought of as an antioxidant, it can also act as a PPARα agonist, and supplemental intakes of 12-18 mg daily produce effects on serum lipid profile analogous to those of PPARα agonist drugs such as fenofibrate [102]. A key effect of PPARα agonists is to boost hepatic production of FGF21, which likely explains why astaxanthin supplementation has been found to increase plasma adiponectin levels [102-108]. Hence, astaxanthin supplementation has the potential to decrease colorectal cancer risk via up-regulation of adiponectin.

Vegan Diets and Exercise Training Down-Regulate IGF-I Activity

Moreover, FGF21 inhibits hepatic production of IGF-I, and plasma IGF-I levels tend to be lower in vegans and those eating low-protein diets [98,109-111]. Colorectal epithelium is responsive to the pro-proliferative impact of IGF-I, and elevated IGF-I has been linked to increased risk for colorectal cancer [112,113]. IGF-I could be expected to boost β-catenin activity via PI3K-Akt signaling. Effective IGF-I activity is decreased by plasma IGFBP-1, which is decreased by the hyperinsulinemia associated with obesity. Aerobic exercise training, in the short term, can increase plasma IGFBP-1 by improving peripheral insulin sensitivity and thereby down-regulating insulin secretion, and in the longer term by opposing inappropriate weight gain [114]. Not surprisingly, it is associated with decreased risk for colorectal cancer [115].

Diets rich in heme iron have been linked to increased risk for colorectal cancer, possibly because this well absorbed form of iron may promote pro-mutagenic oxidative damage [116-118]. Vegan or vegetarian diets do not contain heme iron. Although plant-based diets can be rich in iron, non-heme iron has not been associated with increased risk for colorectal cancer, and its absorption is regulated in line with physiologic need [119].

Overall, these considerations suggest that whole-food fiber-rich quasi-vegan diets can work in various complementary ways to lower colorectal cancer risk - as borne out by global epidemiological experience; age-adjusted risk for colorectal cancer used to be at least several-fold lower in the rural Third World as compared to Western nations, as stressed in the writings of Denis Burkitt and Hugh Trowell [119].

Protective Mechanisms of Calcium, Magnesium, Soy Isoflavones, and Quercetin

The hydrophobic bacterial bile acid metabolite deoxycholic acid (DCA) stimulates proliferation of colon epithelium, exerts mutagenic effects on colon epithelial cells in vitro, and acts as a tumor promoter in rodent models of intestinal carcinogenesis [120-123]. Increased serum levels of DCA have been reported in men with colonic adenomas [124,125]. DCA activates β-catenin signaling in colon cancer-derived cell lines [120,126,127]. This effect is associated with a loss of E-cadherin binding to β-catenin that may reflect activation of c-Src [128,129]. There is considerable epidemiological evidence that high calcium intakes, whether via diet or supplementation, notably reduce risk for colorectal cancer [130-132]. This appears likely to reflect the ability of calcium to form unabsorbable complexes with DCA such that DCA's uptake by colonic epithelium is suppressed and fecal loss of DCA rises [133,134]. It is conceivable that magnesium has a comparable effect, as there is evidence that higher intakes of magnesium are

also associated with decreased colorectal cancer risk – albeit an effect of lesser magnitude than that of calcium [131,135,136]. Including some magnesium while supplementing with calcium may be prudent, as high-dose calcium supplementation in the context of low-magnesium diets may have a negative impact on magnesium status [137].

With respect to the ability of activated ERβ to suppress β-catenin expression, it is notable that, in "physiological" doses obtainable from ample ingestion of soy products, the soy isoflavone genistein acts as a selective agonist for ERβ, with minimal impact on "feminizing" ERα [138]. S-equol, a metabolite of the isoflavone daidzein produced by colonic bacteria, can also act as a selective agonist for ERβ [139]. These facts may explain the lower risk for colorectal cancer associated with high intakes of soy foods or of soy isoflavones in Asian epidemiology [140].

Pharmaceutical inhibitors of CK2 are being pursued an anti-cancer drug candidates, as CK2 activity is elevated in many cancers and works in numerous complementary ways – including β-catenin up-regulation - to enhance cellular proliferation and survival [141-143]. However, it is notable that, in sub-micromolar concentrations, certain flavones and flavonols - including apigenin, luteolin, kaempferol, fisetin, quercetin, and myricetin - can inhibit CK2 [144-147]. This may rationalize numerous studies demonstrating that these flavonoids can retard cancer growth in mouse xenograft models [147]. The pharmaceutical utility of many flavonoids is limited by poor solubility that compromises absorption, as well as rapid conjugation after absorption, so fairly ample intakes may be needed for useful activity. Quercetin has the advantage of ample availability, and certain commercially available soluble derivatives such as isoquercitrin and enzymatically-altered isoquercitrin (employed as an antioxidant food additive in Japan) are capable of enabling far more efficient quercetin absorption [148-151]. A quercetin-enriched diet decreases polyp multiplicity in APC(Min/+) mice, and, in vitro, quercetin or isoquercitrin inhibit the growth and β-catenin activity of colorectal cancer cells [152-156]. Hence, quercetin or its more absorbable derivatives may have practical potential for prevention of colorectal cancer.

High Doses of Folate and Biotin May Boost Protective cGMP in Colon Epithelium

In regard to the tumor suppressor activity of cGMP, colon epithelium is known to express soluble guanylate cyclase activity that can respond to nitric oxide generated by nitric oxide synthase (NOS) activity within these cells or within enteric neurons [157]. Intriguingly, the NOS activity in colorectal cancers has been found to be uncoupled, as indicated by a high ratio of dihydro- to tetrahydrobiopterin [158]. If this effect is present in preneoplastic colon epithelium – likely as a consequence of oxidative stress - then measures which re-couple NOS might be expected to oppose colorectal cancer induction via cGMP. In vascular endothelium, high-dose folic acid has been shown to achieve a re-coupling of eNOS via induction of dihydrofolate reductase, which can reduce dihyrofolate to the active cofactor tetrahydrofolate [159,160]. If high-dose folate has a comparable effect in colorectal epithelium, it might be expected to oppose tumor promotion. In this regard, a controlled clinical trial in which 5 mg folate or placebo was administered daily for 3 years to patients with a past history of colorectal adenomas found that this comparatively high dose of folate reduced risk for recurrent adenomas by about two-thirds [161]. Analogous studies employing lower, more physiological doses of folic acid did not show such definitive benefit.

A more direct way to boost cGMP in colonic epithelium would be to administer high-dose biotin (10 or more mg biotin daily, in divided doses); at this supra-physiological intake, biotin can directly activated soluble guanylate cyclase by 2-3-fold [162-164]. Such a regimen tends to be well tolerated in comparison to NO-releasing drugs, as NO can dose-dependently activate this enzyme by up to a hundred-fold, potentially precipitating severe hypotension. However, it should be noted that high-dose biotin supplementation can interfere with certain clinical assays that employ streptavidin-biotin technology [165]. To the best of our knowledge, high-dose biotin has never been tested in rodent models of intestinal tumor induction; such studies appear to be warranted.

Since phosphodiesterase 5 is expressed in colorectal epithelium, use of long-acting inhibitors of this enzyme such as tadalafil has evident potential for raising cGMP in colorectal epithelium, and thereby diminishing colorectal cancer risk [21].

Summing Up

Up-regulated β-catenin activity plays a key role in driving the induction of the large majority of colorectal cancers. This analysis suggests that lifestyle, pharmaceutical, and nutraceutical measures linked to lower risk for colorectal cancer decrease this risk, at least in part, by down-regulating β-catenin activity in colorectal epithelium. Such measures include ingestion of a whole-food fiber-rich plant-based diet, frequent consumption of cruciferous vegetables, aerobic exercise training, daily administration of low-dose aspirin, metformin treatment (and likely administration of the nutraceutical berberine), and increased ingestion of vitamin D, calcium, and soy isoflavones via diet or nutraceuticals. Furthermore, theoretical considerations suggest that high-dose supplementation with folate and biotin may have potential for suppressing β-catenin activity and decreasing colorectal cancer risk by boosting cGMP production in colorectal epithelium. Sesamol has interesting potential as an antioxidant for colorectal epithelium, and might aid colorectal cancer prevention if it became available as a nutraceutical. Quercetin, and its more soluble and

absorbable derivatives isoquercitrin and enzymatically-modified isoquercitrin, may aid colorectal cancer prevention via CK2 inhibition. Astaxanthin may aid this prevention by boosting adiponectin levels. Development of innovative functional foods or nutraceuticals may make complex chemoprevention strategies for colorectal cancer more practical.

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