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# Chemoprevention in familial adenomatous polyposis

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## Abstract

Familial adenomatous polyposis (FAP) predictably leads to adenomas and eventual adenocarcinomas in the lower gastrointestinal tract and less frequently, the upper gastrointestinal tract. Chemopreventive strategies have been studied in FAP patients to delay the development of adenomas in the upper and lower gastrointestinal tract, as well as to prevent recurrence of adenomas in the retained rectum of patients after prophylactic surgery with colectomy and ileorectal anastamosis (IRA). The nonsteroidal anti-inflammatory drug (NSAID) sulindac and selective cyclooxygenase-2 (COX-2) inhibitor celecoxib reduce polyposis of the retained rectum after colectomy with IRA. Reports of cardiovascular risks of some NSAIDs and selective COX-2 inhibitors have led to promising studies of lower doses in combination with ursodeoxycholic acid, statin, and difluoromethylornithine. Curcumin and eicosapentaenoic acid show efficacy in small clinical trials of FAP chemoprevention. This article will review the concept of chemoprevention and the current clinical literature in FAP chemoprevention.

### Keywords

Familial adenomatous polyposis; Adenomas; Chemoprevention; Sulindac; Celecoxib; Curcumin; Eicosapentaenoic acid

## Introduction

### Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by mutation in the Adenomatous Polyposis Coli (APC) gene, located on chromosome 5 [1]. This germline defect accelerates the initiation of the adenoma–carcinoma sequence, resulting in the development of numerous adenomatous colorectal polyps at young age. Polyposis inevitably progresses to colorectal cancer if left untreated. Given the predictable development of colorectal cancer in patients with FAP, the safest preventative strategy is surgical resection of the colon when polyposis develops. The two main prophylactic surgeries are colectomy with ileorectal anastamosis (IRA) and proctocolectomy with ileal pouch-anal anastamosis (IPAA) [2]. Colectomy with IRA is a straightforward operation with less functional side effects compared to proctocolectomy with IPAA [3]. However, patients who undergo colectomy with IRA are at a 25% risk of developing cancer in the retained rectum after 20 years [4]. These patients require regular endoscopic surveillance to identify and treat recurrent adenomas in the rectum.



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Adenomatous polyps also occur in the upper gastrointestinal tract, especially in the duodenum, and may progress to malignancy, albeit at a lower rate [5]. Regular endoscopic surveillance of the upper gastrointestinal tract usually detects duodenal disease at a premalignant state [2].

### Chemoprevention

Chemoprevention is the use of pharmaceutical or natural agents to prevent or delay the development of cancer in healthy patients. Chemoprevention should ideally be well tolerated, low in toxicity, cheap, and effective. Patients with FAP develop visible, countable, precursor lesions in the form of adenomatous polyps prior to transformation to cancer. Consequently, FAP patients are an ideal group to assess the efficacy of various chemopreventive agents. There are three main roles that chemoprevention can play in patients with FAP: (1) to delay prophylactic colectomy; (2) to prevent cancer development in the retained rectum in patients after colectomy with IRA; and (3) to prevent cancer development in the upper gastrointestinal tract, especially the duodenum. Nonsteroidal anti-inflammatory drugs (NSAIDs), ursodeoxycholic acid, statins, difluoromethylornithine (DFMO), and various dietary supplements have been studied as potential chemopreventive agents (Table 1).

## Lower gastrointestinal tract chemoprevention

### Nonsteroidal anti-inflammatory drugs

NSAIDs have been studied extensively as a chemopreventive agent in patients with FAP. The efficacy of NSAIDs has been demonstrated in clinical trials and animal studies. NSAIDs inhibit cyclooxygenase (COX), a key enzyme in the conversion of arachidonic acid to prostaglandins and other eicosanoids. Prostaglandins appear to play a key role in the adenoma–carcinoma sequence by altering cell adhesion, inhibiting apoptosis, and promoting angiogenesis [6,7]. Elevated prostaglandin levels are found in many premalignant and malignant lesions including colorectal adenomas and adenocarcinomas [8].

There are two cyclooxygenase enzymes present in humans, COX-1 and COX-2. COX-1 is constitutively expressed, but COX-2 is absent under physiologic conditions. COX-2 is increasingly induced in the adenoma–carcinoma sequence [6,7]. The importance of COX-2 in the development of adenomas is demonstrated in the Apc Δ716 mouse, a murine model for human FAP. COX-2 deficiency in these mice partly suppresses the adenomatous phenotype [9]. NSAIDs appear to exert most of their anti-neoplastic effect via inhibition of COX-2. However, other evidence suggests NSAIDs may have an anti-neoplastic effect independent of COX-2 suppression (Fig. 1). Other proposed targets include βcatenin, PPARδ, TGFβ, Ras, and NF-κB [10–14].

### Sulindac

The efficacy of NSAIDs as chemopreventive agents in patients with FAP was first suggested in a non-randomized study of four members of a family with FAP complicated by desmoid tumours. In attempting to treat desmoid tumours with sulindac, an NSAID, the number of adenomas in the retained rectum in three of the patients drastically decreased with oral sulindac. One patient had an intact colon which also responded favourably to the sulindac regimen [15].

This finding was confirmed in a single institution, randomized, double-blinded, placebo-controlled trial conducted by Giardiello et al.. The study involved 22 FAP patients, of which only four had undergone previous colectomy with IRA. In a treatment span of 9 months, 150 mg of sulindac twice a day showed statistically significant reduction in polyp count and

diameter compared to placebo. When only the 18 patients with intact colons were analyzed, the results still remained statistically significant at 3 months, 6 months, and 9 months. However, after the discontinuation of the drug at 9 months, partial recrudescence of polyps was noted. No significant adverse effects were experienced by the study subjects [16].

In a trial involving FAP patients who have undergone colectomy with IRA, sulindac for an average of 63 months significantly reduced rectal polyp number in all 12 patients. Higher-grade adenoma (tubulovillous, villous adenomas) recurrence was also significantly reduced. The most common side effect was rectal mucosal erosions [17]. Several clinical trials have verified these findings (Tables 2 and 3) [16–31].

Given its efficacy in regression of adenomas, sulindac's potential as a primary chemopreventive agent in patients with FAP was studied. Forty-one patients with APC mutations (genotypically affected), who were not yet phenotypically affected, were randomized to placebo or sulindac as a primary prophylaxis against the development of colorectal adenomas. After four years of treatment, no significant difference between the two groups was seen. Adenomas emerged in nine of 21 patients receiving sulindac (43%) and 11 of 20 patients receiving placebo (55%, $p = 0.54$). No significant difference in mean number of polyps or size was noted between the two groups [20]. Of note, patients who were polyp-free had significantly lower prostaglandin levels measured in rectal mucosa after treatment than those who developed polyps [32]. The measurement of mucosal prostaglandin level may be helpful to assess compliance as well as effectiveness of sulindac.

The ultimate goal of chemoprevention in FAP is to prevent the inevitable development of colorectal cancer among these patients. Despite evidence that sulindac may regress adenomas in the rectum after colectomy with IRA, no evidence exists that the drug delays or prevents the development of malignancy in these rectal segments. In fact, several patients maintained on sulindac with polyp regression have developed colorectal adenocarcinoma [33–35].

Sulindac can be given to delay the progression of polyposis in the retained rectum among patients after colectomy with IRA but should be used in conjunction with a strict endoscopic surveillance regimen. Currently, sulindac is not recommended as a primary chemopreventive agent.

### Sulindac sulfone

Sulindac is a prodrug that is metabolized in vivo to sulindac sulfide and sulindac sulfone. Sulindac sulfide has anti-neoplastic effects via inhibition of COX and prostaglandin synthesis which can also results in side effects such as gastrointestinal ulceration and bleeding. Sulindac sulfone (exisulind) does not suppress COX activity yet is able to induce apoptosis in colon adenocarcinoma in vitro [36]. In an azoxymethane-induced colon cancer model, sulindac sulfone reduced the tumour incidence, multiplicity, and tumour burden without significant inhibition of cyclooxygenase, lipoxygenase, or phospholipase $A_2$ [37]. Sulindac sulfone may induce apoptosis via suppression of cyclic guanosine monophosphate (cGMP) phosphodiesterase and subsequent increase in cGMP-dependent protein kinase G with resultant programmed cell death [38].

In a randomized, placebo-controlled study conducted by Arber et al., 281 patients with sporadic adenomatous polyps were given placebo or sulindac sulfone 100 or 200 mg twice per day for 12 months. The higher dose of sulindac sulfone showed significant reduction in median polyp size compared to placebo (50% versus 25%, $p = 0.03$). There was also a lower rate of disease progression in the sulindac sulfone group compared to placebo (6.1% versus 27.9%, $p = 0.02$). However, significant increase in liver enzymes (8.4%) and abdominal pain

(14.7%) were reported in the sulindac sulfone group [39]. Eighteen FAP patients with prior colectomy with IRA were given sulindac sulfone at a dose of 200, 300, and 400 mg orally twice per day. No significant decrease in polyp number or significant effect on cellular proliferation was noted after 6 months of treatment. Reversible hepatic toxicity marked by elevated transaminase and bilirubin was noted in eight of 18 patients, requiring dose reduction or drug cessation. Generally mild gastrointestinal side effects including nausea, vomiting, abdominal pain, indigestion, decreased appetite, and change in bowel habits were reported in 14 of 18 patients [40]. Sulindac sulfone appears to have minimal effect in FAP patients, and is associated with hepatotoxicity.

## Cyclooxygenase-2 inhibitors

Interest in COX-2 inhibitors as chemopreventive agents in FAP was prompted by the gastrointestinal toxicity noted with a long-term use of non-selective NSAIDs [41,42]. Several randomized, placebo-controlled trials with COX-2 inhibitors showed reduction of sporadic colorectal adenoma recurrence[43–45].

In a double-blind, placebo-controlled study, 77 FAP patients (25 with intact colons) were randomized to celecoxib at 100 mg or 400 mg twice daily or placebo for 6 months. Endoscopic evaluation performed at the beginning and end of the 6 months demonstrated a 28% reduction in mean number of polyps ($p = 0.003$) and 30.7% reduction in polyp burden ($p = 0.001$) in the high-dose celecoxib group compared to the placebo group [46].

The efficacy of celecoxib as primary chemopreventive agent was suggested in a study by Lynch et al. involving a cohort of 18 young patients with APC gene mutations and/or adenomas with a family history of FAP. Celecoxib at a dose of 16 mg/kg/day, corresponding to an adult dose of 400 mg twice per day, was well tolerated and significantly reduced the number of colorectal polyps by 44.2% at 3 months ($p = 0.01$) [47]. Although promising, further studies are needed to determine the safety of a long-term COX-2 inhibitor use in children with FAP, and whether this drug can safely delay prophylactic colectomies in these patients.

Despite apparent effectiveness, reports of potential cardiovascular toxicity with COX-2 inhibitors limit their use in FAP. Dose-dependent increase in incidence of deaths from cardiovascular causes, nonfatal myocardial infarction, stroke, and heart failure have been noted in patients receiving COX-2 inhibitors [52–54]. Based on this data, rofecoxib (Vioxx) was voluntarily removed by Merck from the United States market in 2004. Celecoxib remains available but with a United States Food and Drug Administration (FDA)-mandated black box warning. Cardiovascular complications do not appear to be limited to COX-2 inhibitor use. Non-selective NSAIDs, including sulindac and naproxen, have been suggested to increase cardiovascular thrombotic events [55,56].

The benefit of regular use of COX-2 inhibitors and non-selective NSAIDs in FAP patients with cardiovascular risk factors needs to be weighed against the potential cardiovascular adverse events of these medications.

## Aspirin

Given the potential cardiovascular side effects of NSAIDs, focus has turned to aspirin as a candidate for chemoprevention in FAP. Unlike sulindac and COX-2 inhibitors, aspirin not only has a favourable cardiovascular profile but is used as primary pharmacotherapy in patients with cardiovascular risk factors. Several, randomized, placebo-controlled trials have shown reduction in sporadic adenomas in patients using aspirin with prior history of adenomas [57–59].

In the Colorectal Adenoma/Carcinoma Prevention Programme 1 (CAPP1) study, aspirinwas studied in combinationwith resistant starch (RS), a dietary fiber, in patients with FAP. Starch consumption had been described to inversely correlate with colon cancer incidence [60]. In the CAPP1 study, 206 FAP patients with intact colons were randomized to one of four arms: aspirin 600 mg orally daily, RS 30 g orally daily, aspirin plus RS, or placebo plus placebo. After median treatment duration of 17 months, no significant reduction in polyp count or size was noted with either intervention. However, a trend towards a decrease in polyp count and size was noted in the aspirin groups but not the resistant starch groups [61].

With favourable cardiovascular profile, aspirin holds appeal as a primary chemopreventive agent for colorectal cancer, but effectiveness in FAP remains unclear.

## Combination therapy

The concern for potential toxicity of NSAIDs has spurred interest in combination therapy that may allow for lower doses of NSAIDs in patients with FAP. Several animal studies have demonstrated potential roles of these combination therapies.

### Difluoromethylornithine and nonsteroidal anti-inflammatory drugs

Polyamines (putresceine, spermidine, and spermine) are low-molecular-weight, organic cations that are ubiquitous in all higher eukaryotes. They are important for normal cellular growth and differentiation [62]. Polyamine levels are elevated in neoplastic tissues compared to normal tissues and in presymptomatic patients with FAP. Activity of ornithine decarboxylase (ODC), the first enzyme in the polyamine synthesis, is also significantly elevated in presymptomatic patients with germline APC mutations [63]. Difluoromethylornithine (DFMO) is an enzyme-activated irreversible inhibitor of ODC with antiproliferative qualities. The clinical use of DFMO has been limited by side effects found at high doses, including hearing loss, diarrhoea, abdominal pain, emesis, anaemia, leukopenia, and thrombocytopenia [64]. Low-dose DFMO can be combined with NSAIDS to limit toxicity, and the combination inhibits intestinal carcinogenesis in mice and rats [65–68]. In a human study, 375 patients with history of previously removed sporadic adenomas were randomized to receive placebo or combination of DFMO 500 mg and sulindac 150 mg daily for 36 months. Follow-up colonoscopy in 3 years showed significant decrease in recurrence of one or more adenomas in the DFMO/sulindac group ($P < 0.001$). There was also significant reduction in advanced adenomas (8.5% versus 0.7%, $P < 0.001$) and multiple adenomas (13.2% versus 0.7%, $P < 0.001$) in patients receiving the combination therapy versus placebo. No significant difference in adverse events was noted in the trial [69]. Trials comparing celecoxib versus celecoxib and DFMO in patients with FAP are currently under investigation.

### Ursodeoxycholic acid and nonsteroidal anti-inflammatory drugs

Ursodeoxycholic acid or ursodiol is a tertiary bile acid, minimally present in human bile. When given orally, this bile acid decreases rates of colonic neoplasia in rats and patients with ulcerative colitis and primary sclerosing cholangitis [70–72]. Ursodiol has an inhibitory effect on COX-2 [73]. In a study involving $Apc^{Min}$ mice, ursodiol, in combination with low-dose sulindac, caused a dose-dependent decrease in the number of small bowel and colonic polyp tumours. The combined regimen of sulindac and ursodiol was more effective than either agent alone [74].

### Statin and cyclooxygenase-2 inhibitor

Two large randomized, controlled trials studying the effect of hydroxyl-3-methylglutaryl CoA reductase (HMGR) inhibitors or statins on cardiovascular outcomes suggested a

possible role of statins as a colorectal chemopreventive agent. Patients taking pravastatin and simvastatin had 43% and 19% reduction in sporadic colorectal cancer incidence, respectively [75,76]. In a case–control study of 1953 patients with sporadic colorectal cancer and 2015 controls, the use of statins was associated with a significant reduction in relative risk of colorectal cancer [77]. These observations let to animal studies in $Apc^{Min}$ mice, a murine model for human FAP. In $Apc^{Min}$ mice fed a combination of atorvastatin and celecoxib for 80 days, complete suppression of colonic polyp formation and 86% reduction in small intestinal polyps were noted. A synergistic effect occurred with combination therapy significantly greater than that of each agent alone [78].

## Eicosapentaenoic acid

Omega (ω)-3 polyunsaturated fatty acids (ω-3 PUFAs) are naturally occurring fatty acids found predominantly in cold-water fish and include the essential fatty acid α-linolenic acid (ALA) and metabolites eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Epidemiologic studies suggest a role for ω-3 PUFAs as chemopreventive agents. Populations with higher consumption of fish and fish oil as compared to animal fat have lower incidence of colorectal cancer [79,80]. In $Apc^{Min}$ mice, EPA significantly suppressed polyp number and load in both the small and large intestine [81]. Both COX-2-dependent and -independent mechanisms appear to play a part in PUFA's role as a chemopreventive agent [82–85].

West et al. randomized FAP patients with prior colectomy with IRA to either 1 g of EPA twice per day orally or placebo for six months. The group performed endoscopic evaluation of the retained rectum at time 0 and 6 months. At 6 months, there was 22.4% ($p = 0.012$) reduction in polyp number and 29.8% ($p = 0.027$) decrease in polyp size in the EPA group compared to the placebo group. No significant difference in adverse events was reported [86].

## Curcumin

Curcumin (diferuloylmethane) is the major yellow pigment extracted from turmeric, the powdered root of *Curcuma longa*. Turmeric is commonly used as a spice in Asia, especially the Indian subcontinent where a low incidence of colorectal cancer exists [87]. Rodent studies show that curcumin may interfere with colon carcinogenesis [88,89], and $Apc^{Min}$ mice treated with curcumin have reduction in intestinal tumour formation [90]. The mechanism of chemoprevention appears to involve the upregulation of carcinogen-detoxifying enzymes such as glutathione S-transferase [91] and suppression of COX-2 expression [92]. In 15 patients with advanced colorectal cancer refractory to standard chemotherapies, radiologic stability of disease was noted in five patients treated with 2–4 months of curcumin [93].

The combination of curcumin and quercetin, a flavonoid recognized for antioxidant properties, was studied in five patients ranging in age from 21 to 51, who have undergone colectomy with IRA (four patients) or proctocolectomy with IPAA (one patient). In this uncontrolled trial, patients were given curcumin 480 mg and quercetin 20 mg orally three times per day for 3–9 months. This combination was associated with a mean decrease in rectal and ileal polyp number from baseline of 60.4% ($p = 0.043$) and polyp size from baseline of 50.9% ($p = 0.039$). The combination was tolerated well. One patient reported self-limited diarrhoea and another reported mild nausea and sour taste after ingestion of the pill which subsided after 3 days without recurrence [94]. Further randomized, double-blind, controlled studies in humans are needed to confirm these findings.

### Vitamins and minerals

Nearly 30 years ago, Bussey et al. studied Vitamin C's effect upon polyposis. In a study involving 36 FAP patients with colectomy and IRA, patients were randomized to vitamin C 3 g orally daily or placebo for 15–24 months. A non-significant trend towards reduction in rectal polyp number was noted in patients treated with vitamin C [95]. In a 4-year period, combination of daily vitamin C (4 g) and vitamin E (400 mg), with or without grain fiber (22.5 g) supplementation was studied in 58 FAP patients with prior colectomy and IRA. No difference in rectal polyp number was seen in patients taking the vitamins. However, a non-significant trend towards reduction in rectal polyp number was seen in the high-fiber group with increase in reduction in patients who were compliant with the treatment regimen [96].

In a meta-analysis of three randomized trials involving individuals with prior sporadic adenomas, supplemental calcium was effective for the prevention of recurrent adenomas [97]. However, in a trial involving 25 patients with FAP with prior colectomy and IRA, daily calcium carbonate at 1500 mg orally showed no effect on the number, size, or distribution of rectal polyps [98].

## Upper gastrointestinal tract chemoprevention

Since colorectal cancer can largely be prevented by prophylactic colectomy and regular polyp surveillance in the retained rectum, duodenal cancer has become the leading cause of death in patients with FAP who have already undergone prophylactic colectomy [99]. Nearly 90% of patients with FAP will develop duodenal polyps, the precursor lesions of duodenal adenocarcinoma [100] and 4.5% will develop duodenal adenocarcinoma in their lifetime [5]. In contrast to the colon, prophylactic surgical resection of the ampulla and/or duodenum is accompanied by significant morbidity. Duodenal surgery is currently indicated for patients with severe duodenal polyposis or duodenal carcinoma. Chemoprevention would be ideal to induce regression or stabilization of these premalignant lesions.

Twenty-four FAP patients with prophylactic colectomy and advanced duodenal polyposis were randomized to sulindac at 200 mg orally, twice daily or placebo. After 6 months of treatment, no significant qualitative improvement in duodenal polyposis was seen compared to placebo [18]. However, there were significantly fewer small polyps, 2 mm or less, noted in the sulindac treatment compared to placebo group [101]. In a study comparing the efficacy of sulindac to calcium and calciferol in 18 patients with upper gastrointestinal polyps with prior colectomy, no significant change in polyp number was seen in either group after 6 months of treatment [102]. A prospective study composed of eight patients with prior large duodenal polyposis, were given sulindac 150 mg orally twice per day for a mean of 8.75 months. No significant benefit was seen in these patients, and one developed an invasive periampullary carcinoma while on sulindac [103].

Phillips et al. randomized 83 FAP patients to receive 100 mg celecoxib twice daily, 400 mg celecoxib twice daily, or placebo. After 6 months of treatment, there was no significant difference among the groups in number of polyps. However, there was significant qualitative improvement in polyposis for those taking the high-dose celecoxib when the patient's endoscopies were reviewed independently by five physicians [104]. Despite this positive study, chemoprevention studies of duodenal polyposis with NSAIDs have been disappointing (Table 4). Resistance of FAP duodenal polyposis to NSAIDs in contrast to FAP colorectal polyposis may, in part, be explained by differential COX-2 expression. COX-2 is expressed at higher levels in the duodenum than colon in FAP patients [106]. Thus, higher dosages of NSAIDs may be needed to suppress polyposis in the duodenum. However, future studies with higher dosages may be limited by the potential cardiovascular toxicity of non-selective NSAIDs and COX-2 inhibitors [52–56].

Along with positive effect on colonic polyposis, EPA and combination NSAIDs with DFMO, ursodiol, or statin reduce small intestinal polyposis in $Apc^{Min}$ mice and show promise as potential chemopreventive candidate regimens in humans for duodenal polyposis [67,74,78,81].

## Summary

Many drugs and dietary supplements have been studied as potential agents for chemoprevention in familial adenomatous polyposis. The NSAID sulindac and the COX-2 inhibitor celecoxib have been studied most extensively and show efficacy in reducing polyp burden in patients after colectomy with IRA. Celecoxib also shows benefit in patients prior to colectomy and possibly in patients with duodenal polyposis.

Chemoprevention with sulindac 150 mg twice daily or celecoxib 400 mg twice daily can be considered in FAP patients following initial prophylactic surgery and retained rectal segments as an adjunct to endoscopic surveillance. It is unclear whether Celecoxib 400 mg twice daily is beneficial in patients with duodenal polyposis. The benefits of these agents in long-term use need to be closely weighed against the risk of potential gastrointestinal and cardiovascular side effects. Any use of chemopreventive agents requires vigilant endoscopic surveillance as breakthrough malignancies are documented in patients despite being maintained on a chemopreventive regimen.

Combination therapy with NSAIDs along with dietary supplements such as curcumin and PUFAs shows promise as chemopreventive agents but needs further randomized, controlled trials to verify efficacy and safety. As knowledge in the pathophysiology of FAP advances, more effective drugs and drug combinations will no doubt present themselves as potential chemopreventive agents.

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**Key points**

- The NSAID sulindac and COX-inhibitor celecoxib can reduce adenoma burden in the retained rectum of patients after colectomy with ileorectal anastamosis.
- The COX-2 inhibitor celecoxib may reduce diminutive duodenal adenomas.
- Although chemopreventive agents cause polyp regression, whether alteration of the progression to adenocarcinoma occurs is unclear, as case reports exist of patients developing malignancy despite chemopreventive regimens.
- If utilized, chemopreventive regimens should be accompanied by vigilant endoscopic surveillance and supplemented by ablation therapies.
- Combination therapy and dietary supplementation show promise in reducing polyposis in animal studies and small human trials.

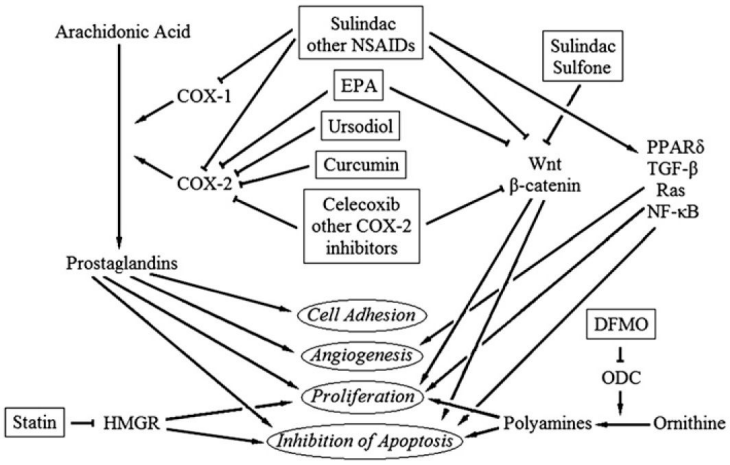


**Fig. 1.**
Mechanisms of chemoprevention.

**Table 1**

Potential chemopreventive agents in FAP

| |
|---|
| NSAIDs |
| Sulindac |
| Celecoxib |
| Aspirin |
| Combination therapy with NSAIDs |
| Difluoromethylornithine |
| Ursodiol |
| Statin |
| Eicosapentaenoic acid |
| Curcumin |
| Vitamin C |
| Fiber |
| Calcium |

## Table 2

Randomized, placebo-controlled clinical trials of lower gastrointestinal tract chemoprevention in FAP patients

| Ref. # | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| [16] | Giardiello | 22 | All patients had history of polyposis. 18 patients had intact colons. Four patients had undergone subtotal colectomy with ileorectal anastamosis. | Sulindac 150 mg twice a day | 9 months | At nine months, sulindac group had decrease in number of polyps by 56% ($p = 0.014$) and size of polyps by 65% ($P < 0.001$). 3 months after the discontinuation of sulindac, there was increase in number and size of polpys. | None observed |
| [18] | Labayle | 10 | All patients had history of colectomy and ileorectal anastamosis. | Sulindac 100 mg three times a day | 4 months | Statistically significant decrease in rectal polyps in sulindac vs. placebo ($P < 0.01$). Recurrence of polyps after discontinuation of sulindac. | None observed |
| [19] | Nugent | 24 | All patients had advanced duodenal polyposis and previous prophylactic colectomy. | Sulindac 200 mg twice a day | 6 months | Rectal polyps improved in five of seven patients ($p = 0.01$) taking sulindac. Duodenal polyps improved in five of 12 patients ($p = 0.12$) taking sulindac. | One patient stopped sulindac for indigestion within 6 weeks. |
| [20] | Giardiello | 41 | Genotypically affected FAP patients without polyposis at time of randomization. | Weight 20–44 kg – Sulindac 75 mg twice a day. Weight >44 kg – Sulindac 150 mg twice a day | 48 months | No significant differences in the mean number or size of polyps between sulindac and placebo. Five of 21 withdrawn from sulindac group and six of 20 withdrawn from placebo group. | Few adverse effects. One withdrawn from study for possible drug-induced persistent neutropenia. |
| [46] | Steinbach | 77 | All patients had five or more polyps at randomization. Twenty-five had intact colons. | Celecoxib 100 mg twice daily or 400 mg twice daily | 6 months | Mean number of colorectal polyps reduced by 28% ($p = 0.003$), rectal polyps reduced by 22.5% ($p = 0.01$), and polyp burden reduced by 30.7% ($p = 0.001$) in the high-dose celecoxib group compared to placebo. | No significant difference in adverse events among low-dose celecoxib, high-dose celecoxib, and placebo. One patient withdrew from study due to dyspepsia. Another |

| Ref. # | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | | | | | | | patient withdrew due to acute allergic reaction. Another patient with prior psychiatric history committed suicide. |
| [47] | Lynch | 18 | All patients, aged 10 to 14 years-old, had APC mutations and/or adenomas with family history of FAP. | Celecoxib 16 mg/kg per day | 3 months | Reduction in colorectal polyps by 44.2% ($p$ = 0.01) | No significant difference in adverse events between celecoxib and placebo. |
| [48] | Higuchi | 21 | Thirteen patients had previous colectomy with IRA. | Rofecoxib 25 mg daily | 9 months | At 9 months, 9.9% decrease in polyp number compared to placebo ($p$ = 0.004) and reduction in polyp size compared to placebo (−16.2% versus 1.5%, $p$ < 0.001). | No significant difference in adverse events. |
| [49] | Iwama | 61 | All patients had diagnosis of FAP as defined by 100 or more adenomas in the colon and rectum. Twenty-four patients had intact colons. | Tiracoxib 150 mg daily or 200 mg daily | 26 weeks | No significant difference in polyp number or size noted between tiracoxib and placebo group | No difference in adverse events noted between tiracoxib and placebo group |
| [61] | Burn | 206 | All patients were young patients aged 10 to 21 years-old, who had confirmed FAP-associated APC mutation or high probability of carrying the mutation based on linked DNA markers or presence of mlutiple colonic polyps. All patients had intact colons. | Aspirin 300 mg twice a day and/or resistant starch 15 g twice a day | Median 17 months | No significant reduction in polyp count in the rectosigmoid colon with aspirin or resistant starch. Trend towards smaller size of largest polyp in aspirin compared to nonaspirin group (3.8 mm versus 5.5 mm, $p$ = 0.09). Significant decrease in largest polyp size in aspirin group compared to nonaspirin if treated >1 year (3.0 mm versus 6.0 mm, $p$ = 0.02). | No serious adverse effects recorded. One patient withdrew from aspirin/ resistant starch group due to persistent epistaxis. |
| [86] | West | 55 | All patients had previous colectomy with ileorectal anastamosis. | Eicosapentaenoic acid 1 g twice daily | 6 months | Number of rectal polyps reduced by 22.4% ($p$ = 0.012) and sum of polyp | No significant difference in adverse events between eicosapentaenoic acid |

| Ref. # | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | | | | | | diameter reduced by 29.8% ($p$ = 0.027). | and placebo. |
| [95] | Bussey | 36 | All patients had previous colectomy with ileorectal anastamosis. | Vitamin C 3 g daily | 15–24 months | A non-significant trend towards reduction in rectal polyp number noted in vitamin C compared to placebo group at 9, 12, and 15 months. | None reported |
| [96] | DeCosse | 58 | All patients had previous colectomy with ileorectal anastamosis. | Vitamin C 4 g and Vitamin E 400 mg daily or grain fiber 22.5 g daily | 4 years | No difference in rectal polyp number between Vitamin C/E group and placebo. Trend towards decrease in rectal polyp number in fiber group compared to placebo at 9 and 33 months. | Diarrhoea more frequent in fiber group ($p$ < 0.05). |
| [98] | Thomas | 25 | All patients had previous colectomy with ileorectal anastamosis. | Calcium carbonate 1500 mg daily | 6 months | No significant difference in rectal polyp number, progression, or distribution between calcium and placebo group. | None reported |

## Table 3

Non-randomized clinical trials of lower gastrointestinal tract chemoprevention in FAP patients

| Ref.# | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| [17] | Cruz-Correa | 12 | All patients had previous colectomy with IRA. | Sulindac mean dosage of 158 mg daily | 14–98 months | At 12 months, 74% reduction of polyp number ($p$ = 0.02). Significant reduction of high-grade adenomas ($p$ = 0.004). One patient developed stage III rectal cancer after 35 months | Rectal mucosal erosions in six patients. |
| [21] | Waddell | 10 | Four patients had intact colons. | Sulindac 150 mg or 200 mg twice a day | 12-85 months | Decrease or disappearance of polyps in all patients. | None reported |
| [22] | Rigau | 7 | Three patients had FAP. One patient had Gardner syndrome. One patient had non-familial adenomatous polyposis. Two patients had multiple hyperplastic polyposis. | Sulindac 200 mg twice per day | 12–36 months | Reduction in number and size of polyps after 6 months in all patients. No development of carcinoma during follow-up. | None observed |
| [23] | Spagnesi | 20 | Fourteen patients had previous colectomy with IRA. Six had intact colons. | Sulindac 100 mg twice per day | 60 days | Significant decrease in size and number of polyps ($p$ < 0.01) | None reported |
| [24] | Ishikawa | 6 | Five patients had FAP. One patient had more than 30 colorectal adenomatous polyps. | Sulindac 300 mg daily | 6 months | Three of six patients had reduction in polyp number. | One patient developed multiple ileorectal anastamotic ulcers despite reduction in dose. One patient had perforation of a gastric ulcer. One patient had oligospermia improved after stopping sulindac. One patient had subcutaneous abscess. |
| [25] | Winde | 28 | All patients had previous colectomy with IRA. | Sulindac 150 mg suppository twice a day with dose reduction | 3–48 months | All patients had reduction in polyposis at 24 weeks. | No withdrawals due to adverse effects. Two patients had mild gastritis. |

| Ref.# | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| [26] | Tonelli | 15 | All patients had previous colectomy with IRA. | Sulindac 100 mg t wice per day | 12–124 months | Significant regression of polyps after 6 months in all patients ($p < 0.02$). Polyposis increased. After a mean of 48.6 months, number and size of polyps increased again with statistical difference with baseline. One patient developed rectal cancer after 106 months. | One patient withdrew due to gastric bleeding after 49 months. |
| [27] | Fernandez-Lopez | 29 | All patient had previous colectomy with IRA. | Sulindac 150 mg twice a day | 6 months | All patients had regression of polyps after 6 months except for one patient who eventually developed rectal cancer. | None reported |
| [28] | Guldenschuh | 17 | Seven patients had previous colectomy with IRA. | Sulindac 300 mg daily | 4 months | Statistically significant decrease in number of adenomas (120 ± 112 to 28 ± 64, $p = 0.007$). Six months after cessation of therapy, number of adenomas increased to 48 ± 44.5. | None observed |
| [29] | Matsumoto | 7 | No patients had prior proctocolectomy. | Sulindac 100 mg three times per day | 12 months | Protrusion index measured by double-contrast barium enema examination improved from 3.0 ± 1.1 to 1.1 ± 0.8/$cm^2$ in distal colon ($p < 0.02$) and from 3.4 ± 2.4 to 0.9 ± 1.3/$cm^2$ in proximal colon ($p < 0.02$). | None observed |
| [30] | Hirota | 8 | All patients had previous colectomy with IRA. | Indomethacin suppository 50 mg once or twice per day | 4–8 weeks | In six of eight patients, number of polyps decreased. Number of polyps increased after | Tenesmus occurred in one patient after suppository insertion. |

| Ref.# | First author | Patients | Patient characteristics | Treatment regimen | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| | | | | | | indomethacin discontinuation. | |
| [31] | Akasu | 7 | All patients had prior colectomy with IRA | Indomethacin sustained-release 75 mg–100 mg daily | 81–345 days | Reduction of rectal polyp number seen in all patients ($p$ = 0.023). Increase in size and number of rectal polyps after cessation of treatment in six patients after a median of 373 days. | Two patients had anaemia due to lower intestinal ulcers and treatment discontinued. |
| [50] | Dolara | 7 | All patients had previous colectomy with IRA. | Nimesulide 2 mg/kg per day | 2.5 months | No change in mucosal proliferation by biopsy | One patient had generalized oedema and muscle pain. |
| [51] | Hallak | 8 | Five patients had previous colectomy with IRA. | Rofecoxib 25 mg daily | 18–30 months | Reduction in polyp formation from 15.1 ± 11.7 to 6.0 ± 5.8 after 12 months ($p$ = 0.002) and further decrease to 1.6 ± 1.6 at end of follow-up ($p$ = 0.001). | No major side effects |
| [40] | van Stolk | 18 | All patients had previous colectomy with IRA. | Sulindac sulfone 200 mg, 300 mg, or 400 mg daily | 6 months | No significant decrease in polyp number or cellular proliferation. | Reversible hepatotoxicity noted in eight of 18 patients. |
| [94] | Cruz-Correa | 5 | Four patient had previous colectomy with IRA and one patient had previous proctocolectomy with IPAA | Curcumin 480 mg and quercetin 20 mg three times per day | 3–9 months | Decrease in rectal and ileal polyp number by 60.4% ($p$ = 0.043) and size by 50.9% ($p$ = 0.039) from baseline. | One patient had self-limited diarrhoea and, another patient reported mild nausea and sour taste with treatment. |

## Table 4

Clinical trials of duodenal polyposis chemoprevention in FAP patients

| Ref. # | First author | Type of study | Patients | Study drug | Duration | Outcome | Side effects |
|---|---|---|---|---|---|---|---|
| [19] | Nugent | Randomized, double-blind, placebo-controlled | 24 | Sulindac 200 mg twice a day | 6 months | Qualitative polyp status improved in five patients, worsened in one and was unchanged in five ($p = 0.12$ compared to placebo) | One patient stopped sulindac within 6 weeks due to indigestion without endoscopic evidence of duodenal ulcer or erosion. |
| [102] | Seow-Cheon | Randomized crossover, double-blind | 18 | Calcium carbonate 380 mg/ calciferol 500 mg daily or sulindac 300 mg daily | 6 months | No significant difference in gastric or duodenal polyposis noted in either treatment group. | Not reported |
| [103] | Richard | Prospective | 8 | Sulindac 150 mg twice a day | Mean 8.75 months | No significant benefit seen. One patient progressed to invasive duodenal adenocarcinoma. Another patient showed recurrence of polyp with severe dysplasia requiring a pancreaticoduodenectomy. | Two patients discontinued sulindac due to abdominal cramps. Another stopped due to documented gastritis, duodenal ulcer, and progression of polyps to villous changes. |
| [104] | Phillips | Randomized, double-blind, placebo-controlled | 83 | Celecoxib 100 mg or 400 mg twice a day | 6 months | When reviewed by five endoscopists, celecoxib 400 mg twice daily showed qualitative improvement in duodenal polyposis ($p = 0.033$). No quantitative improvement seen. | One patient had an allergic reaction to celecoxib. Second patient withdrew from study with symptoms of dyspepsia without evidence of peptic ulcer. Another with psychiatric history committed suicide. |
| [105] | Wallace | Randomized, placebo-controlled | 26 | Ranitidine 300 mg daily | 6 months | No difference seen in duodenal polyp number compared to placebo ($p = 0.9$). | None reported |