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REVIEW ARTICLE

# Stem cell targeting efficacy of dietary phytochemicals in colon cancer

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## ABSTRACT

**Background:** The standard of care treatment options for colon cancer include the use of conventional cytotoxic chemotherapy and/or molecularly targeted pathway selective pharmacological agents. These long-term treatment options are associated with systemic toxicity, acquired phenotypic resistance and emergence of chemo-resistant cancer initiating stem cell population. These limitations favor metastatic disease progression, compromise patient compliance, and thereby, emphasize identification of testable therapeutic alternatives for chemo-therapy resistant colon cancer. Naturally-occurring dietary phytochemicals exhibit low systemic toxicity, human consumption and preclinical efficacy. These natural products may provide potential alternatives.

**Objectives:** The present mini-review provides a systematic discussion of published evidence relevant to i) preclinical cellular models for colon cancer, ii) development of colon cancer stem cell models, iii) stem cell targeting efficacy of dietary phytochemicals and iv) applicability of present experimental approach to identify dietary phytochemicals as testable treatment alternatives for therapy resistant colon cancer.

**Conclusions:** Isolation and characterization of drug resistant stem cell models provide experimental systems to examine stem cell targeting efficacy of dietary phytochemicals for chemo-therapy resistant colon cancer. Phytochemical-mediated growth inhibition validates experimental approaches to identify mechanistic leads for efficacious phytochemicals and prioritize these agents for further investigations.

**Future Research:** Published evidence defines a scientifically robust rationale for future research on patient derived tumor samples to reduce extrapolation of preclinical data for their clinical relevance and translatability.

**Keywords:** Stem cells, dietary phytochemicals, colon cancer.

## Introduction

Progression of advanced stage metastatic colon cancer represents a prevalent cause of mortality in male and female population. The American Cancer Society has projected combined colon cancer incidence of 107,320 and cancer related deaths of 52,900 for 2026[1]. It is also noteworthy that post-menopausal patients exhibit substantial risk for colon cancer, identifying potential role of estrogens[2,3]. In this context preclinical cellular models developed from female patients or female animals are likely to provide valuable experimental systems.

Conventional cytotoxic chemotherapy using pharmacological agents functioning as DNA synthesis inhibitors, DNA intercalating agents and topoisomerase inhibitors represent commonly used treatment options[4].

Preclinical studies have provided mechanistic evidence that cyclooxygenase-2 (COX-2) functions as a rate-limiting enzyme for prostaglandin biosynthesis pathway and ornithine decarboxylase (ODC) functions as a rate-limiting enzyme for polyamine biosynthesis pathway, respectively. These pathways are upregulated during colon carcinogenesis. Based on the preclinical evidence molecularly targeted pathway selective small molecule inhibitors functioning as cyclooxygenase inhibiting non-steroidal anti-inflammatory drugs, selective COX-2 inhibitors and selective ODC inhibitors have been used for the treatment of genetically predisposed as well as sporadic colon cancer[5-7]. Long-term treatment with the pharmacological agents is commonly associated with systemic toxicity, acquired therapy resistance and survival of chemo-resistant cancer initiating cancer stem cell population. These limitations compromise patient compliance and favor metastatic progression of colon cancer, and thereby, emphasize identification of stem cell targeting testable therapeutic alternatives.

Unlike limitations for chemotherapy, natural products such as dietary phytochemicals and Chinese nutritional herbs used in traditional Chinese medicine have documented human consumption, low systemic toxicity, preclinical efficacy and low risk of phenotypic resistance[8-11]. These advantages suggest that the natural products may represent testable therapeutic alternatives.

The main objectives of the present mini-review are to provide a systematic discussion of published evidence relevant to i) preclinical cellular models for colon cancer, ii) development of drug-resistant stem cell models, iii) Stem cell targeting efficacy of dietary phytochemicals and iv) applicability of present experimental approaches to identify dietary phytochemicals as testable alternatives for therapy resistant colon cancer.

## Cellular Models

Human colon carcinoma derived cellular models are predominantly developed from sporadic colon cancer in male patients. Published evidence for similar models from female patients is not adequate. These models exhibit somatic mutations in the tumor suppressor adenomatous polyposis coli (APC) gene and/or in APC-regulated β-catenin gene. In addition to sporadic colon cancer genetically predisposed familial adenomatous polyposis (FAP) syndrome and hereditary non-polyposis colon cancer (HNPCC) also exhibit high risk for colon cancer. FAP syndrome is notable for chromosomal instability and aneuploidy, while HNPCC exhibits microsatellite instability and diploidy[12-16]. Published evidence for human tissue derived cellular models for FAP and HNPCC is not adequate.

Animal models carrying germline genetic defects in APC and /or in DNA mismatch repair genes provide valuable systems for FAP and HNPCC. Cellular models developed from colonic epithelium from APC mutant female mice and from double mutant DNA mismatch repair Mlh1 and APC mutant female mice exhibit spontaneous immortalization, hyper-proliferation and tumorigenic transformation. These cellular models for FAP and HNPCC provide valuable experimental systems wherein to examine the role of clinically relevant genetic defects for tumorigenic transformation, Wnt/β-catenin signaling, DNA mismatch repair

defects and mechanisms of action of chemo-preventive efficacy of pharmacological agents as well as natural products[17,18]. The molecular characteristics of cellular models derived from human and mouse colonic epithelial cells are summarized in Table 1.

**Table 1.** Cellular Models for Colon Cancer

| Model | Human Colon Carcinoma Genotype APC β-catenin | Mouse Colon Epithelial Cells Genotype Apc Mlh1 | Origin | Clinical Subtype |
|---|---|---|---|---|
| HCT-116 | WT MT | | Somatic Mutation | Colon Cancer |
| SW480 | MT WT | | Somatic Mutation | Colon Cancer |
| SW640 | MT WT | | Lymph Node Metastasis | Colon Carcinoma |
| HCA-7 | MT WT | | Somatic mutation | Colon Adenoma |
| C57 COL | | +/+ +/+ | Descending Colon | Normal Colon |
| 1638N COL | | +/- +/+ | Apc Colon | FAP |
| $850^{MIN}$ COL | | +/- +/+ | Apc Colon | FAP |
| Mlh1/1638 COL | | +/- -/- | Mlh1/Apc Colon | HNPCC |

WT, wild type; MT, mutated; APC, adenomatous polyposis Coli; Mlh1, Mut.L1; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colon cancer.

## Stem Cell Models

The Wnt/β-catenin signaling pathway is essential for regulating normal homeostatic growth control in colonic crypts[19,20]. Disruption of this pathway and activation of cell survival pathways via RAS oncogene (RAS),phospho-inositol-3-kianse (PI3K) , protein kinase B (AKT), and molecular target for Rapamycin (m TOR) signaling has been demonstrated in cancer stem cell phenotypes[21-23]. Cancer specific expression of these signaling pathways may represent potential therapeutic targets that may be susceptible to pharmacological inhibitors as well to natural bioactive agents present in dietary phytochemicals and nutritional herbs.

Cellular models developed by using colonic epithelium isolated from APC mutant APC 1638N COL, $850^{MIN}$ COL and from Mlh1/1638N COL female mice exhibit hyper-proliferation, accelerated cell cycle progression and downregulated cellular apoptosis *in vitro,* and tumor formation on in vivo transplantation. The APC mutant cell lines represent models for genetically predisposed familial adenomatous polyposis (FAP) syndrome at risk for colon cancer. The cell line that carries mutation in Mlh1 and APC genes represent a model for hereditary non-polyposis colon cancer (HNPCC). These cell lines have been used to develop drug resistant cancer stem models. In the parental cells, as well as in stem cell models, it is notable that genetic defects in APC signaling results in upregulated expression of APC target genes β-catenin, cyclin D1, cellular Myc (c-Myc), cyclooxygenase -2 (COX-2) and peroxisome proliferator activating receptor-Δ(PPAR-Δ)[12-14]. The genetic defects in the HNPCC model include abnormal expression of DNA mismatch repair genes[15-18,24.]

## Sulindac resistant model:

Non-steroidal anti-inflammatory drugs represent commonly used treatment options as pathway selective molecularly targeted therapy of colonic adenoma. Prolonged treatment commonly leads to spontaneous/acquired resistance and emergence of chemo-resistant cancer initiating stem cells[5,6]. Treatment with the non-steroidal anti-inflammatory drug sulindac (SUL) selectively promotes the growth of resistant SUL-R cells[25]. The SUL-R phenotype exhibits increased incidence of the stem cell specific biological marker tumor spheroid (TS) formation, and upregulated expression of the molecular markers clusters of differentiation CD44, CD133 and the transcription factor/oncogene

cellular Myc. The molecular markers are routinely monitored by the cellular uptake of fluorescently labelled antibodies and are quantified as cellular fluorescence relative to isotype control. In comparison to sulindac sensitive cells, the SUL-R cells exhibit upregulation of TS, CD44, CD133 and c-Myc. Evidence for characterization of $850^{MN}$ SUL-R stem cell model is summarized in Table 2.

**Table 2.** Status of Stem Cell Marker Expression in Sulindac Resistant $850^{MIN}$ COL Model

| $850^{MIN}$/SUL-R | Relative to SUL-S |
|---|---|
| TS | + 3.1X |
| CD44 | + 5.0X |
| CD133 | + 5.0X |
| c-Myc | +66.7% |

SUL-R, sulindac resistant; TS, tumor spheroid number; CD44, cluster of differentiation 44; CD133, cluster of differntiation133; C-Myc, cellular Myc. Expressed as relative fluorescent unit (RLU). (Data summarized from reference number 17).

## Fluoro-uracil resistant model:

Conventional chemotherapy for sporadic and genetically predisposed colon cancer includes the use of fluro-uracil, carboplatin, cis-platin and irinotecan[4]. These pharmacological agents frequently promote the emergence of chemo-resistant cancer initiating stem cells. Treatment with the DNA synthesis inhibitor fluoro-uracil (FU) to Mlh1/1638 COL cells provided FU resistant FU-R cells. Relative to the drug sensitive cells, the FU-R cells exhibit upregulated expression of TS, CD44, CD133 and c-Myc[18]. Molecular characteristics of Mlh1/1638 FU-R stem cell model are summarized in Table 3.

**Table 3.** Status of Stem Cell marker Expression in Fluoro-uracil resistant Mlh1/1638 COL Model

| Mlh1/1638/FU-R | Relative to FU-S |
|---|---|
| TS | + 8.6X |
| CD44 | + 5.8X |
| CD133 | + 6.5X |
| c-Myc | + 3.0X |

FU-R, fluoro-uracil resistant; TS, tumor spheroid number; CD44, cluster of differentiation 44; CD133, cluster of differentiation133; C-Myc, cellular Myc. Expressed as relative fluorescent unit. (Data summarized from reference number 18).

## Dietary Phytochemicals

Mechanistically distinct dietary phytochemicals containing polyphenols, flavones, terpenes and omega-3 fatty acids inhibit Wnt/β-catenin, NOTCH and Hedgehog signaling pathways and cancer cell survival pathways including PI3K, AKT, m TOR and nuclear factor kappa B (NFkB) [8-11]. These pathways may also represent potential therapeutic targets for bioactive agents present in nutritional herbs.

Preclinical efficacy of dietary phytochemicals curcumin (CUR), epigallo catechin gallate (EGCG), resveratrol (RES) and genistein (GEN) that contain polyphenols and flavones and terpenes has been documented colon cancer stem cells[10]. These dietary phytochemicals have also been tested in clinical trials for their safety and efficacy on patients at high risk for cancer. In these trials efficacy of these agents on Wnt-β-catenin signaling and PI3K, AKT, m TOR and NFkB pathways have been demonstrated[26-28].These multi-targeted cell signaling and cancer cell survival pathways play essential role in colon cancer stem cell survival. For example, in the Wnt/β-catenin pathway mutation in the adenomatous polyposis coli (APC) tumor suppressor gene dysregulates nuclear translocation of β-catenin and upregulates the expression of target genes cyclin D1 and c-Myc[12-14]. Growth factor receptor mediated activation of PI3K, AKT and m TOR is responsible for stem cell proliferation, invasion

and survival[20-22]. Inflammatory cytokine mediated activation of NFkB pathway involves nuclear translocation of p65 and p50 and expression of the target gene cyclooxygenase -2 (COX-)[23].

Preliminary evidence for the inhibitory effects of select phytochemicals on stem cell specific TS formation is summarized in Table 4. This evidence provides a basis to examine their effects on molecularly targetable stem cell markers such as downstream signaling proteins that are functional in Wnt/β-catenin, Notch and hedgehog pathways.

**Table 4.** Effect of Phytochemicals on tumor Spheroid Formation in Sulindac resistant $850^{MIN}$ /SUL-R Model

| Treatment | TS Number (Inhibition % control) |
|---|---|
| CUR | 83.9 |
| EGCG | 68.8 |
| EPA | 68.7 |
| DHA | 64.5 |
| CA | 55.9 |

TS, tumor spheroid; CUR, curcumin; EGCG, epigallocatechin gallate; EPA, eicosa-pentaenoic acid; DHA, docosa hexaenoic acid; CA, carnosic acid. (Data summarized from reference number 24).

The data presented in Table 5 provides evidence for the efficacy of curcumin (CUR), the bioactive agent present in turmeric and of the vitamin A derivative all-trans retinoic acid (ATRA) to downregulate the expression of stem cell specific biological and molecular markers.

**Table 5.** Phytochemical mediated modulation of stem cell marker expression in $850^{MIN}$ /SUL-R model

| Treatment | Stem Cell Marker Expression (Inhibition % Control) | | | |
|---|---|---|---|---|
| | TS | CD44 | CD133 | c-Myc |
| CUR | 80.4 | 69.4 | 68.1 | 44.3 |
| ATRA | 69.0 | 74.7 | 69.4 | 57.3 |

CUR, curcumin; ATRA, all-trans retinoic acid; TS, tumor spheroid; CD44, cluster of differentiation44; CD133, cluster of differentiation133; c-Myc, cellular Myc. (Data summarized from reference number 17).

## Conclusion

Reliable epithelial cell culture models facilitate mechanistic studies directly on the target cells representing carcinoma. Development of drug resistant stem cell models for FAP and HNPCC and evidence for stem cell targeted efficacy of selected dietary phytochemicals validate reliable experimental systems to identify bioactive agents as potential cancer stem cell targeting drug candidates for therapy resistant colon cancer.

Published evidence relevant to the theme of the present review has also revealed major limitations that emphasize resolution of several unmet needs and unanswered questions. These limitations include i) lack of appropriate cellular models that investigate the role of estrogens in colon cancer, ii) conceptual significance of reliable models from patient-derived tumor samples, and iv) inadequate evidence from network pharmacology and structure-activity guided investigations on dietary phytochemicals affecting Wnt/β-catenin and DNA mismatch repair signaling pathways. Experimental strategies addressing these limitations are likely to strengthen the role of dietary phytochemicals in prevention/therapy of colon cancer.

Collectively, at the conceptual and technical levels published evidence and intrinsic limitations provide a scientifically robust rationale for future research directions.

## Future Research

In colon cancer progression adenoma to carcinoma sequence represents common process wherein adenoma is a recognized pre-neoplastic lesion and a biological endpoint for carcinogenesis and cancer prevention. The drug resistant stem cell models for FAP and HNPCC facilitate mechanistic studies on stem cell targeting efficacy of nutritional herbs. Use of stem cell models from therapy resistant patient derived colon explants (PDTX) and patient derived colon tumor organoids (PDTO) and application of novel mechanistic endpoint biomarkers as discussed below may facilitate reduction of data extrapolation and support of their clinical relevance and translatability.

**Estrogen receptor-β expression:** In estrogen receptor signaling α and β receptors function reciprocally as positive and negative growth regulators for receptor expressing cells and may represent valuable therapeutic targets[29], Incidence of Post-menopausal colon cancer emphasizes the applicability of relevant models. In the female Apc $^{MIN}$ /+ mice estrogen receptors modulate the incidence of colon adenoma formation[30]. Bioactive agents such as polyphenols, flavones, terpenes, lignans and saponins may also influence phyto-estrogenic activity of nutritional herbs predominantly via binding to the ER-β response element and modulating downstream target gene expression[8,11]. In this context investigations on FAP and HNPCC stem cell models developed from female mice facilitate examination of the role of natural phyto-estrogens as ER-β agonistic agents.

**Telomerase expression:** Expression of the nucleo-protein enzyme telomerase represents a universal marker for immortalized cancer stem cells[31,32]. Thus, telomerase expression may represent a therapeutic target for dietary phytochemicals and nutritional herbs.

**Epigenetic modifiers:** Epigenetic modulation involves post-translational modification of nuclear histones, DNA synthesis enzymes and gene promoter methylation. In these processes one-carbon metabolism functions as a predominant methyl donor[33,34]. Dietary phytochemicals and nutritional herbs may represent testable alternatives to examine their effects on histone methylation, DNA methyltransferase and methylation of CpG islands in gene promoter regions.

**Epithelial-mesenchymal transition:** Cellular plasticity of cancer stem cells is responsible for epithelial-mesenchymal transition (EMT), a recognized hallmark of metastatic stem cell phenotype. EMT-MET reversible process favors metastatic invasion and niche formation at distant sites, respectively[35,36]. Reciprocal modulation in the expression status of EMT markers vimentin, E-cadherin, and transcription factors SNAIL, SLUG and ZEB provide valuable quantitative end points to examine the effects of dietary phytochemicals and bioactive agents present in nutritional herbs on drug-resistant cancer stem cells.

**New drug candidates:** The bioactive agents from dietary phytochemicals may represent potential drug candidates. Identification of new drug candidates involves multiple sequential steps for screening and prioritization. Network pharmacology, molecular docking, genomic, proteomic metabolomic and transcriptomic in vitro assays on PDTO models represent valuable experimental systems to reduce data extrapolation for clinical relevance and translatability[37]. Effective agents are subjected to safety and efficacy via absorption, disposition, metabolism and excretion (ADME) based in vivo assays. These assays monitor tumor development and their molecular analysis using PDTX models[38,39].

## Conflicts of interest statement:

The author has no conflicts of interest to declare.

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