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Nutraceuticals in Colon Cancer: Emerging Evidence, Mechanistic Insights and Clinical Applications

Abhinandan R. Patil*, Salman Ballari, Ammar Bagwan, Anushk Chougule, Harshwardhan Chougale, Sanika Chougale, Pallavi Chougule, Sakshi Latkar, Saniya Bhandari, Sonali Diwate, Chandraprabhu Jangme

D. Y. Patil Education Society (Deemed to be University), Kolhapur-416006, India

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KEYWORDS

Nutraceuticals; Bioactive compounds; Colorectal cancer; Chemopreventive agents; Polyphenols; Probiotic; Dietary fiber; Cancer prevention

ABSTRACT:

Colorectal cancer (CRC) is the second most common cause of cancer-related death worldwide. Recent evidences review these forms of nutraceuticals, originating from food sources as considerable chemopreventive and therapeutic potential in the management of colon cancer (CC).

Background: This general review aims to provide an overview of the role of these bioactive substances in colon cancer preventative and therapeutic strategies with special emphasis on molecular pathways, and the exploration of scientific and practical evidence-based data for their integration into cancer management.

Materials and methods: A systematic literature review using the PubMed, Web of Science and Google Scholar databases, of publication from 2018-2025. Keywords: Nutraceuticals, Bioactive compounds, Polyphenols, Probiotics, Dietary fiber, Colon cancer, Colorectal cancer, Prevention Studies were assessed at both preclinical and clinical levels.

Summary: Various nutraceutical classes possess inhibition potential against cancer through the modulation of several pathways (e.g., PI3K/Akt/mTOR), induction of apoptosis, arrest of the cell cycle, and stimulation of the immune system. Several mechanisms are potentially involved in this favorable association including the effects of the dietary fiber, polyphenols (curcumin, resveratrol, EGCG), probiotics, and certain micronutrients in both primary and adjuvant prevention. Nonetheless, its clinical translation has been limited, numerous trials examining efficacy and optimal dosing are underway.

Conclusions: Preclinical evidence is more persuasive and only incomplete in clinical evidence for nutraceuticals in colon cancer. The next frontier in colon cancer therapy is a rational and personalized strategy that incorporates safe and available evidence-based nutraceuticals along with standard oncological care, informed by biomarker-guided selection and a rigorous clinical evaluation.

1. Introduction

1.1 The epidemiology and burden of colorectal cancer

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy worldwide, with nearly 1.96 million new cases and 920,000 deaths predicted each year based on newer epidemiological data[1]. The incidence rates are more than 40 per 100,000 population in developed countries whereas in developing regions increasing incidence associated with westernization of diet and lifestyle changes[2]. CRC management, including surgery, chemotherapy, radiation, and supportive care costs billions of dollars annually in the major healthcare systems[3].

Surgical resection, systemic therapy and advances in screening programs (colonoscopy, fecal immunochemical testing) have all improved outcomes in colorectal cancer, however still 30–40% of patients will present with recurrent disease or primary treatment failure[4]. Current standard-of-care approaches—with neoadjuvant chemoradiation followed by radical resection and adjuvant fluoropyrimidine-based chemotherapy—exhibit significant toxicity burdens on health-related quality of life. Thus, a strong case can be made for complementary and integrative approaches to increase the effectiveness of treatment and decrease side effects [5].

1.2 Idea of Nutraceuticals and Bioactive compounds

Describing food-derived substances with pharmaceutical properties, the term nutraceutical was invented in 1989[6]. Nutraceuticals are bioactive compounds at the interface between nutrition and pharmaceutical science, which exert a biological effect that go beyond basic nutrition to provide disease prevention or therapeutic effects[7]. Some Examples: Common Nutraceutical Classes in Cancer Research

Polyphenol Compounds: Flavonoids, phenolic acids, stilbenes, and ligans that come from plant sources

Dietary fibres: soluble and insoluble prebiotic fibres

Probiotics and Microbiota Modulators: Probiotics (Live beneficial bacteria and fermented food products)

Micronutrients : Vitamins and minerals with antioxidant and immunomodulatory properties

Phytonutrients: Bioactive constituents of plants demonstrating cancer specificity

1.3 Background to Nutraceutical Research in Colon Cancer

The following reasons lend themselves to more stringent investigation of nutraceuticals in colon cancer:

Epidemiological Evidence——Strong positive correlation between geographical disparity and dietary pattern, populations adhering to traditional plant-based diets show low incidence rate of CRC[8]

Mechanistic Plausibility: Nutrient-responsive signaling cascades (Wnt/β-catenin, MAPK/ERK, PI3K/Akt/mTOR) are well-characterized to reflect bioactive compound targets[9]

Preclinical Evidence: Many nutraceuticals demonstrate in vitro and animal model-derived evidence of anti-proliferative, pro-apoptotic, and immunomodulatory effects[10]

Compared with traditional chemotherapeutic agents, nutraceuticals derived from dietary sources exhibit more favorable toxicity profiles;

Patient Demand: 60–80% of cancer patients use complementary and alternative medicine and many without physician guidance [11,12]

Clinical Needs Not Previously Funded through an Existing Adjuvant Program: Toxicity from chemotherapy, biologic approaches to therapy, and rates of chemotherapy resistance and recurrence of disease highlight the required need for new adjuvant approaches.

Molecular Mechanisms and Pathways of Action of Nutraceuticals

Signalling Pathway (PI3K/Akt/mTOR) in Colorectal Cancer.

The PI3K/Akt/mTOR pathway is an important pathway in colon cancer biology and regulates cell proliferation, survival, metabolism, and autophagy 12. As many as 50% of colorectal cancers demonstrate dysregulation of this pathway by one of several mechanisms, including PIK3CA amplification, PTEN loss, AKT upregulation, or mTOR hyperactivation[13].

Mechanism of Pathway Dysregulation:

Phosphoinositide 3-kinase (PI3K) is activated by growth factor signaling through receptor tyrosine kinases leading to the generation of phosphatidylinositol triphosphate (PIP3) by the phosphorylation of PIP2. PDK1 and mTORC2 subsequently phosphorylate Akt after compartmentalization to the membrane where it is recruited. Pathway activation is further maintained by phosphorylation and inactivation of PTEN and GSK3β by Active Akt. mTOR is associated with two complexes: mTORC1 (rapamycin-dependent) that stimulates protein synthesis and proliferation as well as mTORC2 (largely rapamycin-resistant) that phosphorylates and activates Akt[14].

Nutraceutical Targeting of PI3K/Akt/mTOR:

This pathway is inhibited by different bioactive compounds through different mechanisms:

Howard: Phosphorylated Akt and mTOR downregulation of survivin and Bcl-2[15]: Curcumin Grand, N.A.

EGCG (Epigallocatechin gallate): PI3K and Akt inhibitor; mTOR signalling suppressor[16]

· Resveratrol: Induces PTEN activation, which opposes Akt signaling; decreases mTOR activity[17]

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Quercetin – inhibits receptor for growth factors and inhibits Akt phosphorylation[18]

2.2 Induction of apoptosis and cell cycle modulation

Resistance to apoptosis is a characteristic feature of cancer. Nutraceuticals induce apoptosis via intrinsic (mitochondria) and extrinsic (death receptor) pathways[19].

Intrinsic Apoptotic Pathway:

Reactive oxygen species (ROS) generated by bioactive compounds and subsequent mitochondrial membrane potential (MMP) destabilization followed by release of cytochrome c activate caspase-9 as well as downstream caspase-3/7 activation, resulting in cleavage of PARP[20].

Extrinsic Apoptotic Pathway:

Ligand-death receptor interactions recruit adaptor proteins and initiator caspase-8 (Fas, TNF-R1, TRAIL-R) This then activates the effector caspases directly or through mitochondria pathway amplification[21].

Cell Cycle Arrest:

IntroductionCyclin-dependent kinase (CDK)-inhibitors p21WAF1/CIP1 and p27KIP1 are induced by many nutraceuticals that inhibit cyclin-CDK complex formation and prevent G1/S- or G2/M-checkpoint progression (1). Polyphenols often target cyclin D1 and CDK2/4, resulting in the arrest of the cell cycle progression[22].

Tumor Microenvironment Modulation and Angiogenesis

For any tumor to grow to more than 1-2 mm^3, it requires the formation of new blood vessels (angiogenesis). There are several ways that nutraceuticals can block angiogenesis:

Suppression of Vascular Endothelial Growth Factor (VEGF):

Curcumin, green tea catechins, and resveratrol down regulates HIF-1α expression and VEGF production, which decreases endothelial cell migration and tube formation[23].

Matrix Metalloproteinase (MMP) Inhibition:

Tumor angiogenesis and invasion of the endothelial cells depends on degradation of extracellular matrix, which requires expression of MMP-2 and MMP-9, both of which are reduced by polyphenols [24].

Tumor Microenvironment Alteration:

Nutraceuticals are immune modulators that target the infiltration of immune responders into the tumor microenvironment, with reductions in tumor-associated macrophages and myeloid-derived suppressor cells, while enhancing CD8+ T cell infiltration and activation[25].

2.4 Modulation of Gut Microbiota and Production of Short-Chain Fatty Acids

Increased evidence indicates that commensal microbiota has an important role in the pathogenesis of colon cancer[8]. Nutraceuticals change the microbial composition and metabolite production[26].

Prebiotic Effects of Dietary Fiber:

Fermentable tongues (b-glucans, araoxylans, pectin, inulin) are metabolized by colonic bacteria into short-chain fatty acids (SCFAs)- mainly butyrate, propionate, and acetate [27]. Butyrate exerts anti-cancer effects through:

- HDAC inhibition, histone acetylation, and gene expression changes GPR43/GPR109A signalling that induces differentiation and apoptosis in Colonocytes
- NEXT -> Improvement of tight junction protein integrity and therefore diminished translocation of bacteria
- Expansion of regulatory T cell (Treg) via GPR43 stimulation in intestine-based immune cells[28]

Probiotic and Postbiotic Mechanisms:

Some of these metabolites and/or compounds are produced by beneficial bacteria to:

· Compete with pathogenic organisms for nutrients and mucosal adhesion.

· Generate specific secondary metabolites that have direct anti-tumor effects

· Boost Mucus Layer to Improve Intestinal Barrier Function

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· Regulation of innate lymphoid cells and adaptive immune responses

· Bacteriocins produced with anti-cancer inducing species antimicrobial activity [29]

The Main Classes of Nutraceuticals shown to be Anti-Colon Cancer

3.1 Polyphenolic Compounds

Curcumin (Turmeric)

The key bioactive component of turmeric (Curcuma longa), curcumin, has been widely studied in colon cancer models[30]. Mechanisms include:

Inhibition of NF-κB and STAT3 pathways leading to decreased inflammatory signaling[31]

· Wnt pathway activation inhibited by β-catenin signaling[32]

· Pro-apoptotic protein upregulation (Bax, Bad, caspases)[33] leading to apoptosis

· Cancer cell generation of ROS and oxidative stress[34]

· COX-2 inhibition and prostaglandin E2 synthesis reduction[35]

Clinical data remains limited. CURCALL study is a Phase II trial assessing curcumin with standard chemotherapy in advanced colorectal cancer with early results awaited [36].

Green Tea Polyphenols (EGCG)

Epigallocatechin gallate (EGCG) is the most abundant catechin in green tea, accounting for 25–50% of the dry weight of green tea. Mechanisms in colon cancer:

Blocking signaling pathway mediated by growth factor–EGFR and HER2 inhibition[37]

· Activation of FOXO3a which drives pro-apoptotic gene expression to form the first[38]

· Inhibition of telomerase and telomere shorten in cancer cell[39]

· By anti-angiogenic action through blocking of VEGF pathway[40]

Epidemiological evidence indicates that regular green tea intake (>3 cups per day) is associated with a risk reduction of 20-30% for colon cancer, in particular in East Asian populations[41].

Resveratrol (Red Grapes, Berries)

Resveratrol, the stilbene polyphenol in red grapes, berries, and peanuts, has various anti-cancer mechanisms[42]:

· Activation of SIRT1, facilitating NAD+-dependent deacetylation of proteins associated with cancer[43]

· Modulators of estrogen receptor, affecting hormones-dependent signalling[44]

· PGC-1α-mediated stimulation of mitochondrial biogenesis[45]

· Inhibition of metastasis via reversal of epithelial-to-mesenchymal transition (EMT)[46]

For resveratrol monotherapy at physiologically achievable doses, 40–60% tumor growth inhibition was demonstrated in preclinical models of colorectal cancer[47].

Quercetin and Other Flavonoids

This flavonoid, which is especially rich in onions, apples, and berries, exerts anti-colon cancer via:

· Inhibition of topoisomerase II causing DNA strand breaks[48]

· Inhibition of protein tyrosine kinase and inhibition of growth signaling[49]

• Calcium dysregulation and apoptosis[50]

3.2 Fermentable Fibers and Short-Chain Fatty Acids reduziert

β-Glucans

β-glucans from oats, barley and fungi have β-1,3, and β-1,6 glycosidic linkages. Evidence in colon cancer:

· Lowering of aberrant crypt foci (pre-neoplastic lesions) in animal models[51]

→ Fermentation of short-chain fatty acid and increase butyrate production[52]

· Up-regulation of autophagy markers (LC3B) and apoptosis markers (cleaved caspase-3)[53]

Improve innate immunity by being a modulator in pattern recognition receptors (Dectin-1)[54]

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Resistant Starch

Physiological Effects of Resistant Starch Resistant starch, a type of dietary starch that is not digested in the small intestine, exhibits protective properties against colon cancer:

• Inhibition of colon tumourigenesis by high-fructose corn syrup[55]

· Enhanced SCFA production especially butyrate[56]

· Distorted microbiome with proliferation of favorable taxa[57]

Down-regulation of HK2 (hexokinase 2), suppressing tumor glycolytic metabolism[58]

Pectin and Arabinoxylans

The inhibitory effect of modified citrus pectin and wheat arabinoxylans on the growth of colon cancer cell lines is both dose- and time-dependent[59]. Mechanisms include:

Inhibition of galectin-3, and subsequently cell-cell adhesion and metastasis[60]

Caspase activation that leads to apoptosis induction[61]

Last but not the least, prebiotic actions and consequential SCFA production [62]

3.3 Probiotics and Microbial Modulators

3.3 Mechanisms of Anti-Cancer Activity of Probiotics

Probiotics—live health-promoting bacteria—have several mechanisms by which they exert anti-colon cancer effects:

Direct Antimicrobial Effects:

Bacteriocin and organic acid (lactic acid, acetic acid) production by probiotics suppress growth of tumor-promoting species including Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis[63].

Immunomodulation:

Probiotics reinforce the infiltration and activation of CD8+ T cells in the tumor microenvironment, skew the macrophage population towards an M1 (pro-inflammatory) phenotype, and expand regulatory T cells to dampen excessive immune response[64].

Barrier Function Enhancement:

Probiotics appear to be able to increase the expression of claudin and occludin, which consequently strengthens tight junctions, reducing the translocation of bacterial lipopolysaccharide (LPS) and systemic inflammation[65].

Metabolite Production:

These beneficial bacteria then produce metabolites, such as butyrate, secondary bile acids, and polyphenol metabolites that have direct anti-cancer effects [66].

3.3 Probiotic Strains with Evidence in Colon Cancer

Lactobacillus species:

Various animal models have shown that the Lactobacillus acidophilus, Lactobacillus plantarum, and Lactobacillus rhamnosus can inhibit tumor growth through immune enhancement and through the production of a metabolite [67].

Bifidobacterium species:

Bifidobacterium longum, Bifidobacterium bifidum, and Bifidobacterium adolescentis proliferate with prebiotic fiber supplementation and correlate negatively with colorectal adenoma[68].

Akkermansia muciniphila:

This bacterium, enriched with polyphenol consumption, has a mucus-specialist behavior that favors both barrier integrity and anti-tumor immunity. Lower quantities associate with CRC susceptibility[69].

3.3.3 Clinical Evidence for Probiotics

Another study performed in 2020 showed that administration of probiotic mixture to tumor-bearing mice resulted in significant CT26 colon tumor growth inhibition and enhanced strong CD8+ T cell-mediated immune responses[70]. However, comparatively few human clinical trials exist. Current Phase II studies are focusing on combinations of probiotics as preventive and adjuvant therapies in CRC settings.

3.4 Micronutrients with Emerging Anti-Cancer Evidence

Vitamin D:

Epidemiological data have linked higher vitamin D status (serum 25-OH vitamin D $\geq$30 ng/mL) with a 30–

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40% reduction in risk of colon cancer[71]. These mechanisms are mainly consisting of VDR-mediated differentiation, apoptosis and immune regulation[72]

Selenium:

Selenium exerts antioxidant and anti-inflammatory effects in preclinical colon cancer models[73] through incorporation into selenoproteins (glutathione peroxidase, thioredoxin reductase).

Zinc:

Zinc, through metalloproteins, helps maintain the integrity of intestinal barrier, contributes to the immune competence and modulates polyphenol metabolism[74].

Folate and Methyl Donors:

Folate (vitamin B9) and other methyl donors are needed for DNA methylation patterns and the mitigation of genomic instability related to colon cancer risk[75].

Clinical Evidence and Translation

4.1 Nutraceutical-Containing Diets: Epidemiological Evidence

A Case for Nutraceutical-Rich Dietary Patterns in Colon Cancer Prevention-Prospective Epidemiological Evidence from Large Cohort Studies

Table 1: Epidemiological Evidence for Nutraceutical-Rich Dietary Patterns in Colon Cancer Prevention

Dietary Pattern/Component	Study Population	Risk Reduction	Publication
High dietary fiber intake	European Prospective Investigation into Cancer (EPIC)	40% (95% CI: 28-50%)	[76]
Mediterranean diet adherence	PREDIMED cohort	27%	[77]
Regular green tea consumption	Asian populations	20-30%	[41]
High polyphenol intake	Nurses' Health Study	24%	[78]
Probiotic-rich fermented foods	Prospective cohort	18-22%	[79]
Combined nutraceutical diet	Multiple cohorts	35-45%	[80]

4.2 Clinical Trials and Interventional Studies

Dietary Fiber Interventions:

Results from clinical trials with fiber supplementation alone have been inconsistent. For example, the Polyp Prevention Trial (PPT) involving >2,000 participants randomized to high-fiber diet versus control found no significant difference in adenoma recurrence [81]. Meta-analysis of several fiber trials, however, indicates benefit when fiber comes from whole food sources as opposed to isolated supplements and when combined with other dietary changes[82].

Polyphenol Supplementation Studies:

One Phase II trial tested curcumin in adjuvant setting after the surgical resection of colorectal cancer. Initial data indicate longer progression-free survival and lower levels of inflammation markers when added to standard chemotherapy[83].

Randomized trials of supplementation with green tea extract among high-risk populations note a modest yet significant reduction in adenoma formation (15-22% relative risk reduction)[84].

Probiotic Clinical Trials:

Randomized controlled trials on probiotic supplementation as polyp prevention is limited and showed mixed outcomes, where between 20-30% adenoma incidence reduction was observed in some trials, while others show minimal efficacy [85].

Variations in probiotic strains, dosages, duration and study populations make interpretation difficult.

4.3 Challenges in Clinical Translation

There are multiple reasons for the discrepancy between encouraging preclinical data and disappointing clinical outcomes[86]:

Low bioavailability: despite the great potential as antioxidants, many polyphenols have poor gastrointestinal absorption and are rapidly metabolized, resulting in a limited exposure of active compounds to colon cells[87].

Dose Concerns: While pharmacologically relevant doses are often employed in preclinical studies, these doses far exceed what is achievable with realistic dietary intakes or supplementation doses[88].

Impaired host factors: their important role is shown also by genetic polymorphisms in phase I/II detoxification enzymes, as well as the composition of the gut microbiota, which vary between individuals, leading to differences in nutraceutical metabolism and disposition [89].

There is methodological heterogeneity between studies: Study design, intervention duration, primary outcomes, and follow-up varies, making meta-analysis and clinical interpretation difficult[90].

Publication Bias: Studies with positive results have higher chance of getting published compared to negative or null trials. This could be an important factor causing apparent inflated efficacy[91].

Safety Considerations and Drug-Nutraceutical Interactions

5.1 Overview of the safety of widely used nutraceuticals

Food-sourced nutraceuticals generally show good safety profiles. However, context-specific concerns warrant consideration:

High-Dose Polyphenols:

High levels of polyphenols may have pro-oxidative activities, may produce reactive oxygen species, and may induce genomic instability in some cell contexts [92].

Adverse Effects of Some Prebiotic Fibers on the Gastrointestinal Tract:

A significant increase in fiber consumption results in bloating, abdominal discomfort and diarrhea due to both osmotic effects and bacterial fermentation of fermentable fibers[93].

Probiotic Administration in Immunocompromised Hosts:

Probiotic-induced bacteremia has been reported in severely immunocompromised patients, making its use in this population a matter of caution[94].

5.2 Drug-Nutraceutical Interactions

Some of the nutraceuticals act on oncologic and non-oncologic medications, as follows:

Polyphenols and Chemotherapy:

It works by inhibiting the phase I (CYP3A4, CYP2C9) and phase II enzymes with green tea catechins and curcumin, which then may alter the metabolism and bioavailability of chemotherapy[95]. Depending on drug and context, this could increase therapeutic effects or toxicity.

Vitamin K and Anticoagulants:

Foods high in vitamin K such as fermented foods also possibly work against warfarin[96].

Fiber and Medication Absorption:

Others such as some antibiotics and anticoagulants may be less absorbed when fiber intake is high[97].

5.3 Treatment and Risk Mitigation vs Patient Education

To maximize safety of nutraceuticals in cancer patients, the following strategies are proposed:

But, Full medication reconciliation including supplements

· Genomic evaluation when appropriate

· Administration of nutraceuticals at different time than when chemotherapy is given

· Follow-up to assess response and toxicity

· Use whole food sources preferentially, rather than isolated supplements, when possible

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Biomarker-Guided Personalized Approaches

A new paradigm of precision nutraceutical medicine (PNM)

Instead of a blanket approach, emerging evidence supports a biomarker-guided selection of nutraceuticals[97] according to the individual specificity of the tumor and/or host factors[98].

Tumor-Related Biomarkers:

Table 2: Biomarker-Guided Nutraceutical Selection Framework

Tumor Biomarker	Relevant Nutraceutical	Rationale
High-Wnt/β-catenin signaling	Curcumin, Quercetin	Inhibit Wnt pathway
Microsatellite instability (MSI-H)	Probiotics, Polyphenols	Enhance anti-tumor immunity
CpG Island Methylator Phenotype (CIMP)	Folate, B vitamins, Methyl donors	Support methylation regulation
High-VEGF/Angiogenic phenotype	Green tea EGCG, Resveratrol	Anti-angiogenic effects
PIK3CA mutations/High PI3K/Akt activity	Curcumin, EGCG, Quercetin	Direct pathway inhibition

6.2 Host-Related Biomarkers

Microbiota Composition:

Dysbiotic microbiota (low *Akkermansia, Faecalibacterium, Roseburia*; high *Fusobacterium, Enterococcus*), may preferentially benefit from prebiotic and probiotic interventions[99].

Genetic Polymorphisms:

CYP3A41B, CYP2C923: Variants of cytochrome P450 relevant to polyphenol metabolism Those classified as slow metabolizers achieve relatively high sex steroid concentrations in tissue and may benefit more from lower doses[100].

Immune Profiling:

Low CD8+ T cell infiltration indicates potential targets for nutraceuticals polyphenols, probiotics, β-glucans which enhance immunity in the tumor.

Prospective foundations in precision nutraceutical oncology

Advanced strategies under development include:

Characteristcs of individual metabolites patterns

Fecal metagenomic sequencing for detailed profiling of microbiota

· Pathway Activation Profiling (pan-elumination)

· AI driven to figure out best combinations of nutraceuticals

Nutraceuticals as add-ons to standard care

7.1 Evidence-Based Integration Framework

Instead of replacing traditional oncology, nutraceuticals should be embedded in comprehensive, multimodality treatment protocols, as adjuvant elements:

Pre-operative Phase (4-8 weeks prior):

· Enhance barrier function and microbiota composition

· Keep promoting dietary pattern changes focused on plant foods, fiber, and polyphenols

Start Probiotic, Prebiotic in their diet if appropriate

Perioperative Phase:

· Ensure a support of fibre and micronutrients for healing and immunity

· Schedule it away from anesthetic agents

Promote adequate nutritional status with enteral nutrition, focusing on protein, micronutrients

Adjuvant Chemotherapy Phase:

· Time nutraceuticals such that they do not affect bioavailability of chemotherapeutics

· Use nutraceuticals supportive of the immune system (((probiotics, polyphenols, β-glucans))) between cycles of chemotherapy

· Check for interactions; titrate to tolerability

Post-Treatment Surveillance Phase:

· Highlight long-term dietary changes as the most effective preventive measure

Consistent use of probiotics and prebiotic fiber

· Check and supplement nutritional deficiencies

Funnel more consumption of polyphenol-rich foods

7.2 Patient Selection and Counseling

Here are example of submission candidates for integration of nutraceuticals:

· Patients interested in alternative methods

· Individuals who show detrimental reaction to conventional treatments

· Patients who would like adjuvant risk reduction options

· For long-term prevention in patients in remission

Counseling should emphasize:

· Clinical Evidence for Select Nutraceuticals

· Maintaining realistic expectations on effectiveness

· Interaction with medicines

· Whole food sources whenever possible

Continued conventional monitoring and therapy is essential

7.3 Monitoring and Assessment

Several parameters that should be monitored during integration of nutraceuticals include:

· Nutritional status (anthropometrics, micronutrient biomarkers)

Inflammatory markers (CRP, TNF-α, IL-6)

Microbiota composition (if available then by stool testing)

· Same routine for tumor markers and imaging

· Tolerance to the treatment and quality of life

· Adherence to medications and interactions

Existing Shortcomings, Constraints, and Directions for Future Research

8.1 Critical Research Gaps

Lack of Large-Scale Randomized Trials:

There is an abundance of preclinical evidence, but few large randomized controlled trials of nutraceuticals in colon cancer prevention and treatment. Ongoing studies include:

· CURECOLON study: Curcumin with 5-fluorouracil

POLYPHENOL-CRC trial: a multi/polyphenol intervention in populations at risk

PROBIOTIC-COL trial: Fixed probiotic association in adjuvant setting

Mechanistic Studies in Human Subjects:

Only a small number of studies utilize biomarker measurement and mechanistic investigation in human populations. Mechanistic insight would be further provided by research employing functional imaging, proteomic Analysis, metabolomics, and immune profiling[102].

Optimal Dosing and Duration:

Supraphysiological doses are used commonly in preclinical studies. Such studies in humans would guide the dosing regimen (balancing efficacy and tolerability) through systematic dose-escalation[103].

Long-Term Follow-Up:

Short-term outcomes (6–24 months) are used in most clinical trials. Longitudinal follow-up beyond 5 years would elucidate the durability of benefit and any late adverse effects.

Future trials — methodological considerations

Standardization Approaches:

Future trials should utilize harmonized protocols for:

Isolation, characterization and quantification of bioactive compounds

· Way of preparing and administering

· Dosing strategies informed by bioavailability and PK data

· Mechanistic rationale for the duration of the intervention

· Assessment of oncologic outcomes and quality of life

Patient Stratification:

Patient selection using biomarkers would render the trial more efficient and clinically relevant. Stratification approaches include:

· Microbiota eubiosis status (eubiotic vs. dysbiotic) [104].

Conclusions and Recommendations

9.1 Summary of Evidence

The present comprehensive review returns evidence that nutraceuticals (bioactive compounds derived from food products) possess a significant scientifically feasible potential as prevention and treatment agents in colon cancer mediated by multi-molecular mechanisms. However, preclinical evidence is compelling in that apoptotic induction, cell cycle arrest, angiogenesis suppression, and immune modulation have all been demonstrated in a myriad of nutraceutical classifications.

Well-posed epidemiological data from large prospective cohorts strongly support dietary patterns focused on polyphenol-rich foods, high fiber, fermented food consumption, and micronutrient sufficiency showing associations with 20 to 45% reduced colon cancer risk.

Nevertheless, clinical evidence is patchy, as most intervention trials reported only small benefits and the evidence is heterogeneous. However, the gap between preclinical promise and clinical translation is large and reflects the non-availability of bioactive nutraceuticals at their sites-of-action, patient-to-patient variation in nutraceutical metabolism, study design heterogeneity and difficulty translating mechanistic learnings to a clinical setting.

9.2 Evidence-Based Recommendations

To Prevent Colon Cancer in People at High Risk:

Dietary Pattern Optimization (Strong Evidence)

Increase consumption of Mediterranean or traditional plant-based diets

o Make the grains you consume totally Whole Grain (>30 g day by day).

Include foods high in polyphenols: colourful veg, blueberries, whole grains, legumes and nuts

o Drink green tea (3–5 cups/day) or match with tea polyphenol

Adding probiotics and prebiotics (Moderate Evidence)

o Use of multi-species probiotic treatment (≥10^9 CFU daily)

o Include prebiotic fiber (inulin, FOS) to help expand good bacteria

Fermented foods (Dairy: yogurt, kaffer; vegetable: sauerkraut, kimchi)

Micronutrient Optimization (Moderate Evidence)

o Maintain sufficient vitamin D levels (30-50 ng/mL serum 25-OH vitamin D)

o Promote ideal folate status through diet or supplementation

o If deficient in some populations consider giving selenium

For the Use of Adjuvants in CRC Survivors:

Polyphenol-Based Interventions (Emerging Evidence)

Add Curcumin supplementation (using black pepper (piperine) to increase absorption)[0.5- 2 g a day in divided doses]

Green tea extract standardized to 50-70% EGCG (up to 200-400 mg daily)

o High-dose resveratrol supplementation (100-500 mg/day) in patients with a priori high risk

Microbiota Support (Moderate Evidence)

o Resumed prebiotic and probiotic treatment after chemotherapy

o Facilitate microbiota restore via dietary pattern optimization

o If feasible, stool microbiota analysis to inform strain selection

Comprehensive Integration (Strong Evidence)

o Use in addition to, not as a replacement for, standard oncologic surveillance and treatment o Watch out for interactions between drugs and nutraceuticals

o Where possible, monitor biomarkers to assess tolerability and efficacy

9.3 PROSPECT AND AN EMERGING PARADIGM

This new paradigm will consider not just generic recommendations, but precision nutritional oncology—biomarker-guided selection of evidence-based nutraceuticals based on individual tumor traits, host factors, and microbiota composition[105].

Development in the next 5–10 decades are likely to unfold in the next ways:

Coordinated [106] standardized nutraceutical products: High quality-controlled, well-characterized botanical and fermented products with known bioactive compound profiles

AI-Guided Selection: Multi-omics data integrated with machine learning algorithms to predict responsivity of indivudals to nutraceuticals[107]

New Broad Spectrum Delivery Systems: Novel Formulations Improving Absorption Ability and Site Specificity by Targeting Delivery to Colonic Epithelium and Long Release of Active Components[108]

Immunotherapy Combination: Checkpoint inhibitors are synergized by microbiota modulation and immune modulation by nutraceuticals [109]

Guidance for Practice: Evidence-based oncology nutrition guidelines for specific nutraceuticals from leading cancer societies (ASCO, ESMO)[110]

9.4 Final Perspective

While quintessential neither panacea nor placebo, nutraceutical remain promising adjuvant agents with a growing body of scientific support. Although the efficacy of single nutraceuticals is infrequently greater than that which can be achieved with standard chemotherapeutics, their collective effect as part of comprehensive multimodal approaches, coupled with good safety, affordability profiles and their cost, renders them a valuable component of the array of cancer care integrated.

The future will require intense clinical testing, mechanistic understanding in humans, product standardization, and fits into precision medicine. With the growing amount of evidence, nutraceuticals are progressively moving from a complementary fringe modality-oriented approach towards an evidence-based oncological practice and will improve the outcome of patients suffering from colon cancer while maintaining a better quality of life.

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