

## Role Of Nutraceuticals In Colon Cancer

**Jesika C. Rane<sup>1\*</sup>**

<sup>1\*</sup>Department of pharmaceutical sciences Apex University, Jaipur Email: ranejesika@gmail.com

**Dr. Jaya P.Sharma<sup>2</sup>**

<sup>2</sup>Department of pharmaceutical sciences Apex University, Jaipur

**Dr. Pankaj K. Sharma<sup>3</sup>**

<sup>3</sup>Department of pharmaceutical sciences Apex University, Jaipur

**Dr. S. M. Sarode<sup>4</sup>**

<sup>4</sup>SSJIPER, jamner, Maharashtra

**Dr. D. K. Kumbhar<sup>5</sup>**

<sup>5</sup>KYDSCT's COP, sakegaon, Bhusawal.

**\*Corresponding Author: Jesika C. Rane**

\*Department of pharmaceutical sciences Apex University, Jaipur Email: ranejesika@gmail.com

### Abstract:

Colon cancer is a world-wide health problem and the most dangerous type of cancer, affecting both men and women. The modern diet and lifestyles, with high meat consumption and excessive alcohol use, along with limited physical activity has led to an increasing mortality rate for colon cancer worldwide. As a result, there is a need to develop novel and environmentally benign drug therapies for colon cancer. Currently, nutraceuticals play an increasingly important role in the treatment of various chronic diseases such as colon cancer, diabetes and Alzheimer's disease. Nutraceuticals are derived from various natural sources such as medicinal plants, marine organisms, vegetables and fruits. Nutraceuticals have shown the potential to reduce the risk of colon cancer and slow its progression. These dietary substances target different molecular aspects of colon cancer development.

**Keywords:** colon cancer, Nutraceuticals

### CANCER

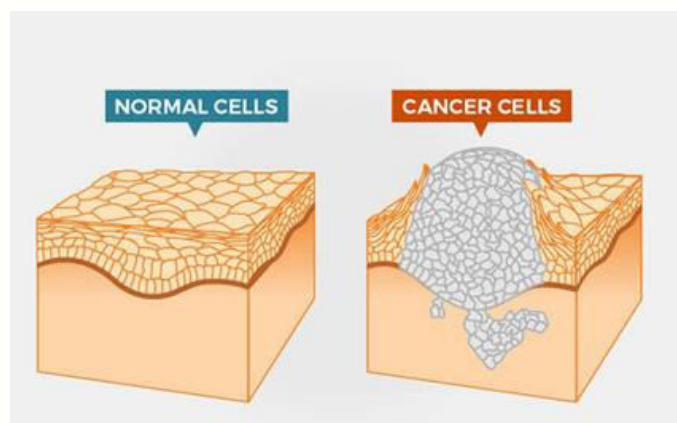
A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems.

Cancer can start anywhere in the human body, which is made up of trillions of cell. Normally, human cells grow and multiply to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Benign tumors do not spread into or invade nearby tissues. When removed, benign tumors usually don't grow back, whereas cancerous tumors can. Benign tumors can sometimes be quite large. Some can cause serious symptoms or can be life threatening, such as benign tumors in the brain. [1]

The name of a cancer is derived from the type of tissue in which it develops. Most human cancers are

- **Carcinomas:** malignant tumors that arise from epithelial cells.

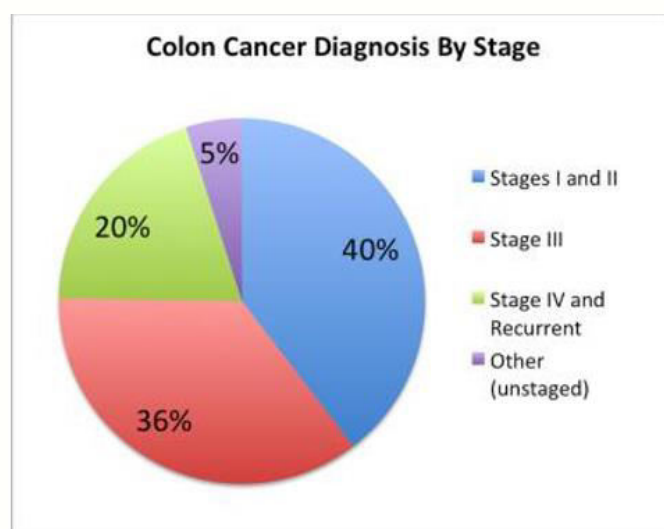
- **Melanomas:** are cancerous growths of melanocytes, skin epithelial cells that produce the pigment melanin.
- **Sarcoma:** is a general term for any cancer arising from muscle cells or connective tissues.
- **Leukemia:** is a cancer of blood-forming organs characterized by rapid growth of abnormal leukocytes (white blood cells).
- **Lymphoma:** is a malignant disease of lymphatic tissue.[2]



### HOW DOES CANCER DEVELOP?

Cancer is a genetic disease, it is caused by changes to genes that control the way our cells function, especially how they grow and divide.

The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer later in life. [1]



### COLON CANCER

Colon cancer is a type of cancer that begins in the colon (large intestine) or rectum. The colon is the final part of the digestive tract.

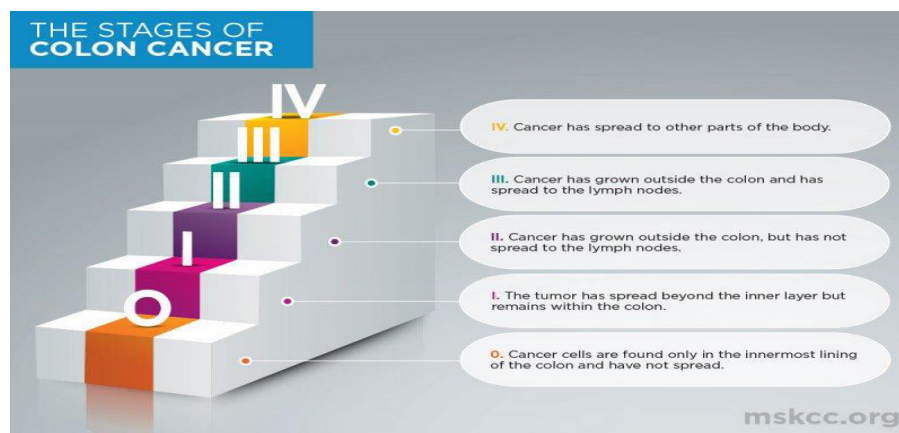
According to the centers for Disease Control and Prevention (CDC) Trusted Source, colon cancer also known as colorectal cancer is the third most common type of cancer in the United States. In fact, the American Cancer Society (ACS) estimates that about 1 in 23 men and 1 in 25 women will develop colon cancer during their lifetime.

## Stages of colon cancer

Stage 0 colon cancer is the earliest stage, and stage 4 is the most advanced stage.

The stages are defined as follows:

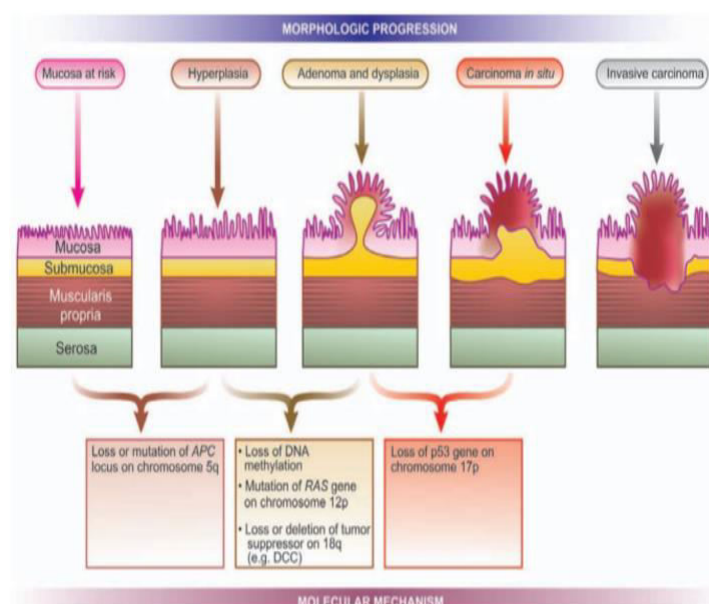
- **Stage 0.** Also known as carcinoma, in this stage abnormal cells are only in the inner lining of the colon or rectum.
- **Stage 1.** The cancer penetrates the lining, or mucosa, of the colon or rectum and may grow into the muscle layer.
- **Stage 2.** The cancer spreads to the walls of the colon or rectum, or through the walls to nearby tissues, but does not affect the lymph nodes.
- **Stage 3.** The cancer has moved across the lymph node but not to other parts of the body.
- **Stage 4.** The cancer has spread to other distant organs, such as the liver or lungs.[3]



## ETIOLOGY

Like many other cancer etiologies, the etiology of colon cancer is not clear but a few etiological factors are mentioned below:

1. Geographic variations.
2. Dietary factors.
3. Adenoma-carcinoma sequence.
4. Hereditary non-polyposis colonic cancer (HNPCC or Lynch syndrome).
5. Other factors.



**1. Geographic variations:** The incidence of colon cancer shows variation across the world. It is much more common in North America, Northern Europe than in South America, Africa and Asia. Colon cancer is attributed to be a disease of affluent societies because its incidence is directly correlated with the socioeconomic status of the countries. In Japan, however, colon cancer is much less common than in the US.

**2. Dietary factors.** Diet plays a significant part in the cause of colon cancer:

- i) A low intake of vegetable fiber-diet leads to low stool bulk, which is associated with higher risk of colorectal cancer.
- ii) Consumption of large amounts of fatty foods by results in excessive cholesterol and their metabolites which may be carcinogenic.
- iii) Excessive consumption of refined carbohydrates that remain in contact with the colonic mucosa for prolonged duration changes the bacterial flora of the bowel, thus resulting in production of carcinogenic substances.

**3. Adenoma-carcinoma sequence:** Colonic adenocarcinoma evolves from preexisting adenomas, referred to adenoma-carcinoma sequence as in the figure.

The following evidences are cited to support this hypothesis:

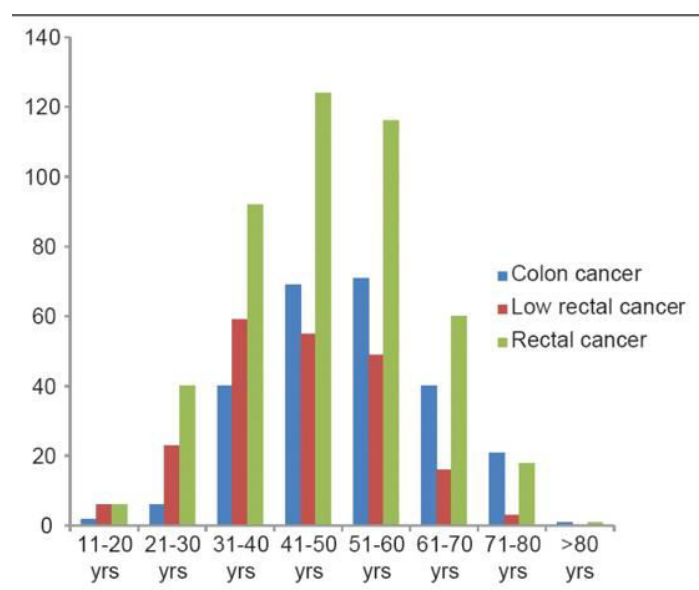
- i) In a case with early invasive cancer, the surrounding tissue often shows *preceding changes* of evolution from adenoma → hyperplasia → dysplasia → carcinoma →invasive carcinoma.
- ii) Incidence of adenomas in a population is directly proportionate to the prevalence of colon cancer.
- iii) The risk of adenocarcinoma colon declines with endoscopic removal of all identified adenomas.
- iv) Peak incidence of adenomas generally precedes by some years to a few decades the peak incidence for colon cancer.
- v) The risk of malignancy increases with the following adenoma- related factors:
  - a) Number of adenomas.
  - b) Size of adenomas.
  - c) Types of adenomas.

**4. Hereditary non-polyposis colonic cancer (HNPCC or Lynch syndrome).** HNPCC is an autosomal dominant condition in which colon cancer is seen in at least two generations of first-degree relatives before the age of 50 years. In HNPCC, colon cancer appears at a relatively younger age (<50 years), associated with multiple primary cancers at different sites (e.g. endometrium, ovary)

**5. Other factors.** Presence of certain pre-existing diseases such as inflammatory bowel disease and diverticular disease for long duration increase the risk of developing colon cancer subsequently. There is an etiologic role of tobacco smoking in development of colon cancer in younger patients.

## PATHOPHYSIOLOGY

Colon cancer can be sporadic, hereditary or from inflammatory bowel disease. Multiple mutation is the primary cause of colon cancer. 94% of colon cancer are due to Sporadic causes, 5% are caused because of inherited mutations and 1% are from inflammatory bowel disease. Normal colon mucosa transforms to adenocarcinoma due to DNA mutations.



### Sporadic

- Genetics alteration in tumor genes results in chromosome instability or suppressor pathway dysfunction.
- Tumors proliferate and grow into cancer because, of mutation in the tumor suppressor genes.
- Mutator pathway dysfunction results in disruption of the DNA mismatch repair (MMR) genes.
- The MMR system identifies an abnormality in the DNA sequence which results in DNA mutation at a rapid pace.
- CpG island methylator phenotype (CIMP) or serrated pathway dysfunction.
- Tumor suppressor genes are inhibited.
- Inhibition of tumor suppressor genes results in the growth of abnormal cells which grow and further develop into colon cancer

### Hereditary

- Lynch syndrome (LS) or hereditary colon cancer.
- Autosomal dominant Defective MMR gene.
- This type of mutation can not only cause colon cancer but can also cause ovarian, gastric, pancreatic, small bowel and sebaceous skin cancers.
- Familial Adenomatous Polyposis (FAP)
- Patients that have inherited FAP have hundreds of polyps in the colon and 100% of patients with this genetic condition will get colon cancer by the age of 40.
- These patient must undergo early screening.
- Autosomal dominant.
- APC gene mutation.

Colon cancer is a slow developing cancer. Altered genes and mutations cause cells to proliferate in the colon and polyps develop in the mucosa. They continue to grow and eventually become malignant and spread to different parts of the body. Polyps can take years to grow into a malignant or cancer causing cell.

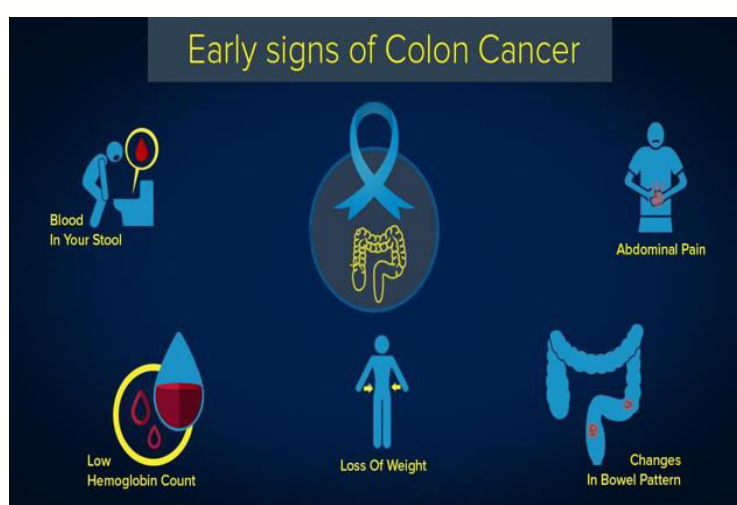
There are different types of polyps:

- Tubular adenoma
- Villous adenoma

- Tubulovillous adenoma
- Sessile serrated
- Hyperplastic[4]

### Signs and symptoms of Colon cancer.

- Anemia.
- Weight loss.
- Weakness.
- Changes in bowel habits.
- Rectal bleeding with bright red blood.
- Fatigue.
- Maroon colored or black stool.
- A feeling that you need to have a bowel movement that is not relieved by having one.



Colon cancer (CRC) is a common cancer worldwide. More than half of the colon cancer cases occur in developed countries but, mortality is higher in less developed countries having limited resources and poor health infrastructure and mortality rates have decreased in developed countries due to early screening and improved treatment of colon cancer. Studies show that it is the third most common type of cancer diagnosed in males and second in females, which accounts to more than 1.4 million new cancer cases every year.

Colon cancer rate in India is 7.2 per 100,000 males and 5.1 per 100,000 women. Studies show that survival rate of colon cancer in India is one of the lowest in the world at less than 40%. [5]

### Nutraceuticals in Cancer therapy

#### Nutraceutical

The term nutraceuticals was coined from “nutrition” and “pharmaceutical” by Stephen De Felice MD, is the **founder and chairman of the Foundation for Innovation in Medicine (FIM)** in 1989, he described nutraceutical as “the food components or active ingredients present in food that have positive effects for well-being and health, including the prevention and treatment of diseases.” [6]

Health Canada defines nutraceuticals as “**a product isolated or purified from food that is sold in a medicinal form that is not associated with food and is demonstrated to have a physiological protective effect against chronic disease**”.



A nutraceutical is any substance considered as a food, or its part which, in addition to its normal nutritional value provides health benefits including the prevention of disease or promotion of health. It is “any non-toxic food component that has scientifically proven health benefits, including disease treatment or prevention”. The functional components of food should be standardized in nutraceutical products and produced under good manufacturing practice (GMPs).

Nearly two third of the world’s population rely on the healing power of plant based material for many reason- availability, affordability, safety or their belief in traditional affordability, or belief in traditional cures. Medical benefits of food has been explored for thousand of years, Modern nutraceutical industry began to develop during the 1980s. according to De Felice, nutraceuticals include foodstuffs, dietary supplements and medical foods, with a distinctive health impact in either prevention and/or treatment of disease. Recent emerging research in nutraceuticals have highlighted its use in prevention and management of chronic diseases, but longer reasearch amd clinical trails are needed to prove its efficacy. [7]

Nutraceuticals are also known as **Functional food**. Functional food are the foods that provide booth health benefits to reduce the risk of chronic disease and basic nutrition.

For food to be considered as functional food it must comply with three specific conditions:

1. Be part of a normal daily diet.
2. Be a natural ingredient, not occurring in the form of pills, capsules, or any medical/ pharmacological form.
3. Once consumed, it has to improve/regulate a specific metabolic process/mechanism, in that way preventing or controlling a disease.[8]

Phytochemicals are defined as **bioactive nutrient plant chemicals in fruits, vegetables, grains, and other plant foods that may provide desirable health benefits beyond basic nutrition to reduce the risk of major chronic diseases.**

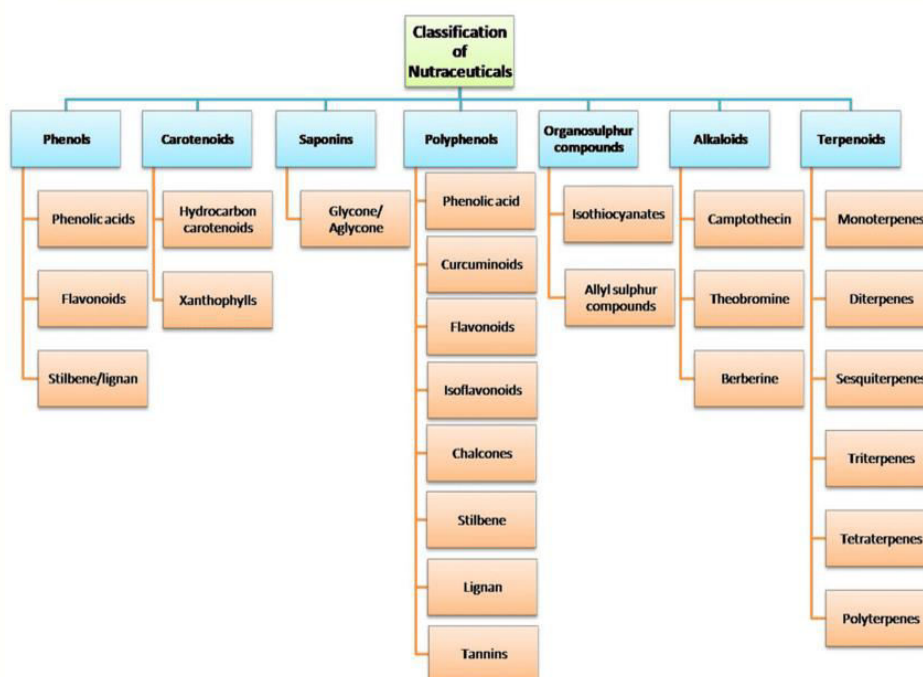
There are various bioactive phytochemicals that play significant role as nutraceutical ingredients. Phytochemicals are mainly obtained from plants, they are the non-essential nutrients showing defensive or disease protective activity in humans.

They have different pharmacological effects such as:

- Antibacterial
- Antifungal

- Chemo-protective
- Anti-inflammatory
- Antioxidants
- Cancer
- DNA damage[9,10]

Plant food contains variety of components that are beneficial for human body micronutrients, polyunsaturated fatty acids and secondary metabolites such as glucosinolates, phytoestrogens, phytosterols, lignans, terpenes, flavonoids, polyphenols, phytates, etc.



### Nutraceuticals in Cancer

Most chronic disease are also categorized as life style disorders and so is **cancer**. The exact cause of cancer is not known and theories project genetic and environmental factors. But **the World Health Organization categorizes cancers as lifestyle diseases** and proposes that faulty lifestyle practices as the predominant predisposing factor for the occurrence of cancers. Dietary habit is one of the most important factors resulting in chronic disease such as cardiovascular diseases, diabetes, several types of cancer, as food has direct impact in health and diseases.

Botanicals have a long history of use in the treatment of cancer. Many cancer chemotherapeutics drug are derived from plants including the alkaloids such as vincristine and vinblastine (of the Vinca species).

Humans have evolved over the years with a sophisticated antioxidant defense mechanism against toxic oxygen intermediates present in air and many other sources.

Epidemiological studies have shown that bioactive plant ingredients such as (nutraceuticals, functional foods and supplemental micronutrients) can reduce cancer cell growth which inhibits cancer cell apoptosis.[11]

Various phytochemicals have anti-cancer properties:

- Vitamin E
- Vitamin C



- Epigallocatechin-3-Gallate(EGCG)
- Curcumin,
- Resveratrol (RES)
- Berberine (BBR)
- Genistein
- Allicin
- Omega-3-fatty acids
- Caffeine

All of the above mentioned have been examined and shown action in cardiovascular diseases, age-related macular degeneration, aging, Alzheimer's disease, colorectal adenoma recurrence, diabetes, defective endothelial function, glucose metabolism/metabolic syndrome, different types of cancer and many other pathologies.[12]

Different phytochemical compounds show different potential pharmacological actions such as:

- Inducing apoptosis of activated T cells and suppress tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin 17 (IL-17)
- Potentially prevent cancer by suppressing the pathway of Nuclear transcription factor correlated with cancer
- Can inhibit cytochrome P450 isoenzyme (CYP1) drug metabolism and cyclooxygenase activity
- Inhibition of cell proliferation, anti-invasive activity, and inhibition of angiogenesis in vitro

Dietary supplement use is highly debated topic, because the efficacy of dietary supplement is not proven and its interaction with the drugs used in cancer is also questionable. 21

Dietary supplements are used by cancer patients in cancer like prostate, colon, lung cancer. Upto 20% to 85% of cancer patients use dietary supplements.

PHYTOCHEMICAL CLASS	BIOACTIVE COMPOUND	SOURCE
Alkaloid	Caffeine Theophylline	Cacao ,tea, coffee Cacao ,tea, coffee
Monoterpenes	Limonene	Citrus oils from orange, lemon, mandarin, lime And grape fruit
Organosulfides	Allicin Indole-3-carbinol Isothiocyanates Sulforaphane	Garlic Cabbage Broccoli Broccoli
Carotenoids	Beta-carotene, Lycopene Epigallocatechin-3-gallate	Tomatoes Green tea
flavonoids	Quercetin  Curcumin Capsaicin	Black tea Turmeric Chill peppers
Phenolic Acids	Ellagic acid Gallic acid	Black berries, raspberry Pomegranate ,nuts
Stilbenes	Resveratrol	Almonds, blueberries, grapes
Isoflavones	Daidzein Genistein	Soy Soy

#### Caffeine:

Caffeine is an alkaloid extracted from coffee grounds or tea leaves. Caffeine is a neuroactive drug. Caffeine enhances migration ability, inhibits apoptosis, decreases acetylation of  $\alpha$ -tubulin, affects

cell cycle functions and may result in upset of key cell cycle regulatory proteins in cancer treatment. Its main function in cancer treatment is its effects on cell cycle and proliferation of cell. Caffeine can be used in combination with DNA- damaging agents in the treatment of cancer as high level of caffeine alone can be toxic for body. Less toxic analogs with biologic activity similar to caffeine should be used. [15]

### Resveratrol:

Resveratrol (**3,4',5-trihydroxy-trans-stilbene**), a polyphenolic compound found in the human diet, generated in response to fungal infection and environmental stress. It is found in variety of plants like grapes, mulberries and peanuts. It is expected to ameliorate cancer.[16] It has shown wide range of health benefits like:

- Boosting immunity
- Anti- obesity effect
- Anti- carcinogenic effect
- Anti- diabetic effect
- Alleviate cardiovascular diseases

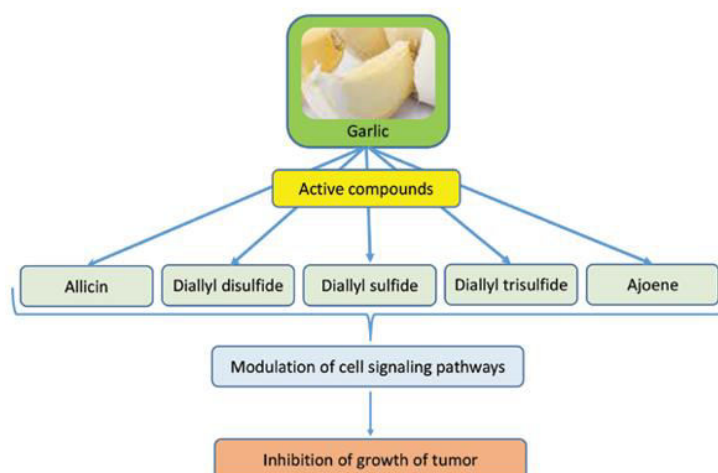
Research is been carried out on its anti- carcinogenic properties, which is extensively focused on its ability to inhibit CYP1A1 gene expression by preventing binding to the aryl hydrocarbon, that regulate transcription; which indeed suppresses the activity of ornithine decarboxylase, enzyme that is responsible for polyamine biosynthesis.[17]

### Curcumin:

Curcumin is a polyphenol derivative extracted from turmeric. Curcumin has a variety of biological activities like antioxidant, antiviral, anti-inflammatory, antimicrobial, anticancer potential [18].Its anticancer potential is still under investigation. It slows the growth of many cancerous tumors. It is proven to be active against stomach, intestine, skin cancer. However as its efficacy is not proven clinical research is needed to be done.[19]

### Diallyl Sulfide:

Diallyl sulfide is a active compound derived from garlic. It has shown to have anti proliferative effect against various types of cancer. It mainly act by the activation of metabolizing enzymes that inhibit the formation of DNA adducts, they show antioxidant effects, regulate the cell cycle, induction of apoptosis which results in cell death [20].



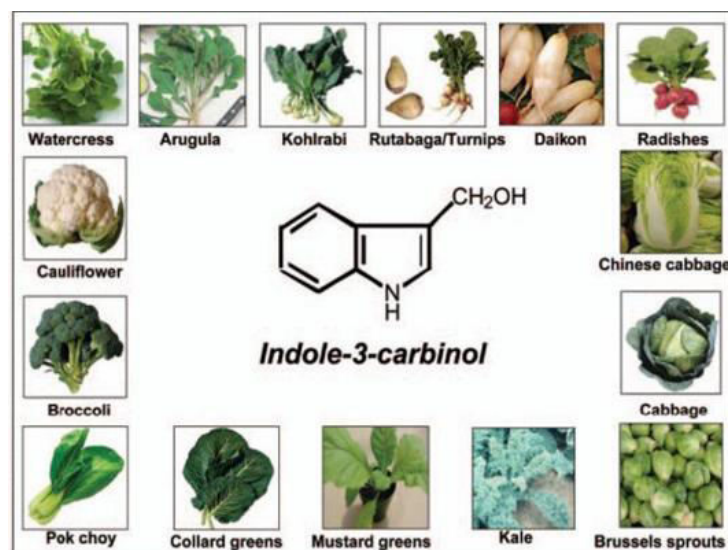
**Vitamin D:**

Vitamin D is an essential for bone health, so does it plays an important role as a anti neoplastic agent. They are mainly conducted via the canonical vitamin D receptor (VDR)-vitamin D response elements (VDRE) pathway. They show there chemo preventive effect by alteration of micro RNA (miRna) expression.[21]

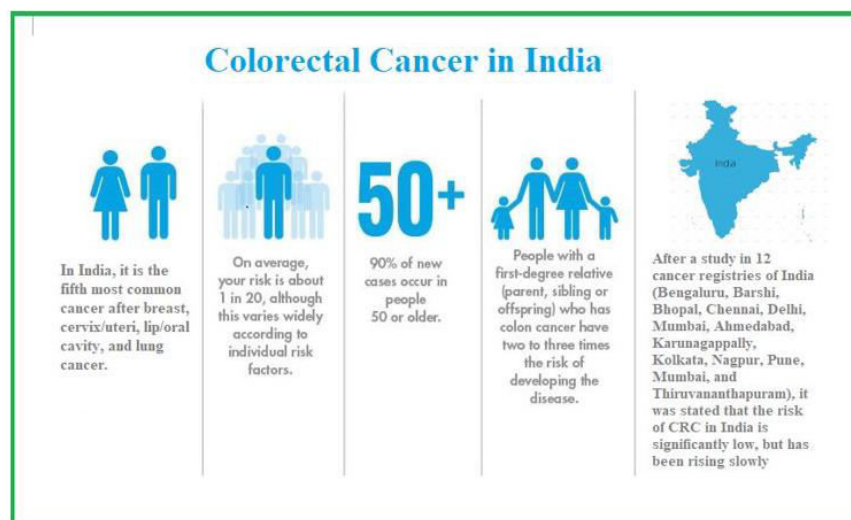
Vitamin D is shown to have potent tumor prevention effect and can induce apoptosis. Vitamin D has body function like regulation of cellular proliferation and differentiation, modulation of immune functions and influence on renin, insulin secretion which are unrelated to calcium metabolism which is associated to vitamin D[22]. Vitamin D is shown to have action in prostate cancer by inducing apoptosis of prostate cancer cells [23].

**Indole-3-carbinol:**

Indole-3-carbinol is a naturally occurring constituent of plants like cabbage, broccoli, cauliflower. They show antitumor effect by various ways such as cell cycle progression, hormonal homeostasis, DNA repair, inducing apoptosis [24]. It has proved to be effective against estrogen-responsive cancers such as breast cancer by altering cytochrome P450- mediated estrogen metabolism [25].

**NUTRACEUTICAL IN COLON CANCER**

**Colon cancer** is the third commonest cancer and the third leading cause of cancer death among men and women. An estimated 1,880,725 people were diagnosed with colorectal cancer in 2020. These numbers include 1,148,515 colon cancer cases and 732,210 rectal cancer cases (American society of clinical oncology). Certain genetic and epigenetic factors have been identified to contribute to the onset of colon cancer. However, up to 70% of all colon cancer cases are sporadic, attributed to environmental factors such as poor diet (i.e. low in fiber and high in fat), metabolic syndrome (i.e. diabetes mellitus, and obesity), and physical inactivity that are mostly associated with industrialization[26]. Indeed, the burden of colon cancer has greatly increased in countries that have adopted the social and economic characteristics of industrialization. Studies in the past decade revealed that such lifestyle associated factors can affect colon carcinogenesis, at least in part, via altering the composition of the gut microbiota, referred to as “dysbiosis”. There is a strong association between changes in the gut microbiota and colon cancer. These changes can prompt carcinogenesis by altering the gut’s metabolic profile, dysregulating the immune response, affecting molecular processes in colonocytes, and instigating mutagenesis.[27]



One way in which the effects of gut dysbiosis can be alleviated is through the application of probiotics and prebiotics. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defined probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” and prebiotics as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon that have the potential to improve host health” [28]. The use of these two types of agents have been known to induce beneficial effects in treating a variety of gastrointestinal conditions. Indeed, according to several studies, medical conditions such as lactose intolerance, antibiotic-induced diarrhea, gastroenteritis, constipation, and genitourinary tract infections can be managed by probiotics. Multiple studies suggest that probiotics, prebiotics, or a combination of two (Synbiotic) can be used to help prevent or even treat colon cancer. In this review, we focus on the potential implications of prebiotics and probiotics in the prevention and treatment of colon cancer through their impact on dysbiosis. We then cover how nutraceuticals can be utilized in colon cancer management in combination with other agents such as immune checkpoint inhibitors [29].

Nutraceuticals have the ability to control DNA damaging factors in cancer cells. Plant derived nutraceuticals are advantageous for the treatment of colon cancer as they have less adverse effect than the other treatment in use for treatment of colon cancer.

### **Role of probiotics, prebiotics and synbiotics in colon cancer**

Several studies indicate the use of prebiotic, probiotics and synbiotics are effective in the treatment of colon cancer. Extensive studies are being carried out on yogurt and lactic acid producing bacteria as they have shown potential cancer prevention properties. Studies indicate that probiotics are the most effective, they can also be used in combination [30].

The mechanism by which probiotic bacteria may inhibit colon cancer is not fully understood. However, there are studies that suggest their action takes place through the:

- alteration of the metabolic activities of intestinal microflora
- production of anti- tumorigenic compounds
- production of anti- mutagenic compounds
- alteration of physicochemical conditions in cancerous cells
- binding of potential carcinogens[31]

### **Production of anti- tumorigenic or anti- mutagenic compounds:**

It is studied that lactic acid bacteria reduces the growth of colon cancer cell line HT-29 and dipeptyl peptidase, this results in cells entering differentiation process[32]. In other studies, fermented milk inhibits the growth of breast cancer cell line. Lactic acid bacteria directly interact with the tumor cell and inhibits its growth.[33]

### **Binding to potential cancer cells:**

Consumption of lactobacilli has been shown to reduce the mutagenicity. Lactobacilli can degrade nitrosamine. Lactic acid bacteria supplements influence the uptake and excretion of mutagens, they have been found to be correlated with the reduction in mutagenicity observed after exposure to the bacterial strains [34].

### **Alteration of physicochemical conditions in the colon:**

There are various factor that may result in colon cancer, they may be influenced by reducing ph of the intestine, thereby preventing the growth of putrefactive bacteria [35]. Dietary fat is also considered a risk factor for colon cancer. This can be mediated by increased levels of secondary bile acids in the colon, producing the action of bacterial 7a- dehydroxylase on primary bile acids [36].

### **Prebiotics:**

Prebiotics are shown to be effective in reduction colon cancer. Garlic, artichoke, onion elevate the level of bifidobacteria. Inulin and oligofructose can recude the severity of 1, 2- dimethylhydrazine induced colon cancer in rats. Studies have demonstrated the capacity of prev=biotic resistant starch type-3 Novelose 330, to reduce the incidence of colon cancer via inducing apoptosis in cancer cells [37].

### **Synbiotics:**

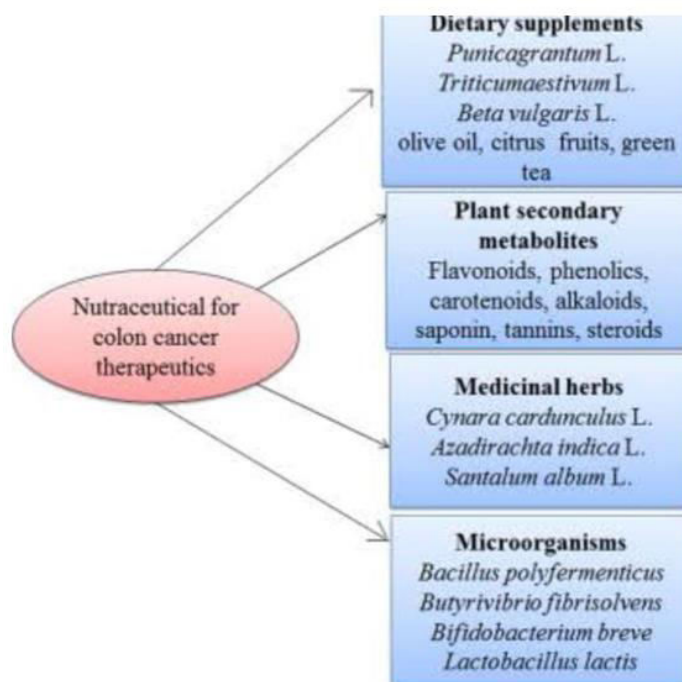
The combination of pro- and prebitoics have a synergistic effect, which is greater than either the pro- or prebiotic administered individually. A combination of inulin and *B. longum* was reported to be more effective at decreasing azoxymethane- induced cancer than they treatment administered individually[38]. This study shows that synbiotics may have a role in colon cancer treatment.

In vitro studies in animal models provide evidence that probiotics, prebiotics and synbiotics have anticancer effects. Their consumption is not only beneficial in treatment of cancer but also in preventing onset of cancer. But there are no substantial evidence of its efficacy in humans as there are no formal clinical trial study performed.

### **Nutraceuticals used in colon cancer:**

- Dietary supplements
- Honey
- Omega- 3 fatty acids
- Vitamins
- Plant secondary metabolites
- Carotenoids
- Flavonoids
- Alkaloids
- Saponin
- Tannins
- Steroids
- Phenolics
- Medicinal herbs
- Microorganisms

- Lactobacillus lactis
- Olive oil
- Green tea
- Citrus fruit peel
- Marine Nutraceuticals
- ◆ Astaxanthan
- ◆ Acetylpoaranotin
- ◆ Siphonaxanthin



### Flavonoids for colon cancer:

Luteolin is found in numerous edible plants and vegetables such as green pepper, celery and perilla. Naturally isolated luteolin secondary metabolites are clinically proven to be effective colon cancer agents. In vivo studies showed that luteolin can decrease tumor incidence and multiplicity in dimethyl benzantraceneinduced papillomas. Also, many in vitro studies have reported that luteolin stimulates apoptosis in several cell lines [39]. Demonstrated that luteolin induced HT-29 cell cycle block, preventing cancer cell growth at the G1/S and G2/M phases. Furthermore, luteolin suppresses the over expression of some antiapoptotic proteins in affected cells and regulates the expression and activity of CDC2 (CDK1) kinase and cyclin B1 proteins, which initiate the G2/M transition phases observed in luteolintreated colon cancer cell lines. Use of moderate concentrations of luteolin significantly increased cancer cell apoptosis. Fisetin is a flavonoid natural substance, occurring in many fruits and vegetables including cucumbers. We observed fasting-induced apoptosis of poly (ADP-ribose) cleavage, which is considered a biomarker of apoptosis. Similarly, caspase-3 was activated in fisetin-treated colon cancer cells. Fisetin can modulate the expression of Bcl-2 metabolites to induce the mitochondrial apoptotic pathway in cancer cells and increases the proapoptotic Bak protein in colon cancer cells [40].

### Carotenoids for colon cancer:

Carotenoids are a major class of secondary metabolites with many biological activities such as free radical scavenging properties, skin tone improvement and potential for cancer treatment. Generally

carotenoids are classified into two main subclasses such as hydrocarbon carotenoids including  $\beta$ -carotene,  $\alpha$ -carotene, lycopene and oxycarotenoids which include lutein and zeaxanthin, as well as other compounds. Carotenoids have many applications in the clinical and commercial fields.  $\beta$ -Carotene has been shown to be efficient in controlling cellular damage from free radicals. Secondary metabolites can influence and effectively react with free radicals in the inner part of the cell membrane. The natural compounds have been more effective in maintaining membrane integrity and antimutagenic properties. The unsaturated nature of lycopene has potential efficiency to provide free radical scavenging activity and inhibit cancer progression. Lycopene is present in various dietary sources such as tomatoes, grapes and papaya. Carotenoids are used for the prevention of colon and gastrointestinal cancer. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a protein that induces apoptosis in cancer cells. TRAIL has been targeted in microtubule formation in the cell cycle. Halocynthiaxanthin is a dietary carotenoid and combined with TRAIL can significantly induce apoptosis in DLD-1 colon cancer cells. The combined drug treatment involves important anticancer effects such as poly (ADP-ribose) polymerase cleavage, induction of caspase inhibitors and nuclear condensation. These mechanisms of halocynthiaxanthin have shown the potential to regulate programmed cell death in colon cancer cells. Other phytochemicals such as xanthophyll, astaxanthin, cryoptoxanthin and zeaxanthin metabolites have been used for the treatment of colon cancer [39].

#### **Polyphenolic clusters for colon cancer:**

Polyphenols are natural phytochemicals used to treat various viral and fungal diseases. They are derived from various sources such as plants, seaweeds, marine algae and microorganisms. Polyphenols includes different organic constituents such as flavones, flavanols, isoflavones, catechins, epigallocatechin-3 gallate (EGCG) and epicatechins. Numerous plants are reported to have polyphenols in their extracts. Polyphenols isolated from tea plants are well studied for their biological properties. Consumption of green tea protects against several types of chemically induced cancer in animal models [41]. Green/black tea is one of the most popular and easily affordable drinks in the world. It has important active metabolites and antioxidant compounds to enhance the health benefits. Green tea contains a high amount of antioxidant polyphenols which effectively controlled cancerous growth in both in vitro and in vivo models. Green tea contains many phytochemicals such as heterocyclic amines, flavones and saponins, and can alter the xenobiotic metabolizing enzymes. These metabolites induce the signal transduction pathway which leads to induction of apoptosis and cell cycle arrest. Some studies have asserted that the high consumption of black tea is also associated with reducing the risk of digestive track cancers[42]. Curcumin is one of the most important secondary metabolites for anticarcinogenic properties and is already used clinically. Curcumin affects the molecular level of protein expression in colon cancers such as COX-2, VEGF, IL-1, IL-6, IGF and Chemokines. The drug targets the active site of COX-2 in malignant cells and it modulates the action of TNF- $\alpha$  and NF- $\kappa$ B factors. Likewise, curcumin is well known clinically as a chemopreventive agent used during the initiation and progression stages of digestive tract cancer. Curcumin inhibits the secretion of gastrointestinal hormones such as neurotensin. Human colorectal cancer cell line HCT 116 treated with curcumin altered the hormone neurotensin action and induced the IL-8 expression in a time- and dose-dependent manner [43].

#### **Dietary supplements for colon cancer prevention:**

Nutraceutical products and their active metabolites effectively suppress a wide range of colon cancer cell lines, namely HCT-116, HT-29, SW 480, SW 620, CaCo2 and LoVo. In vitro studies of various antioxidant fruits including black raspberry, strawberry, and grape seeds were proven to reduce intestinal tumors [44]. Garlic has a diverse nutritional profile and is used to treat common and endemic diseases. Garlic contains various dietary ingredients such as organosulfur and S-allylcysteine compounds. It is a main precursor for inhibiting the growth of colon cancer in a

clinical model. Rats used for experimental studies by oral administration of garlic extract exhibited decreased multiplication of cancer cells in the initiation stage, but during the late stage the extract was not effective. Also the extract has no clear scientific evidence for cancer preventive efficacy. Garlic extract also has some toxicity, increasing hemolysis and increasing the anemic condition of the patient. Fenugreek has high content of diosgenin, and it belongs to the steroidal group of saponins. Its cancer-preventative mechanisms have not been fully studied. So far some activity of the fenugreek crude extract supported the anti-proliferation activity against leukemia, colon and breast cancer cell lines [45].

### **Omega-3 fatty acids:**

Fatty acids are long chain hydrocarbons which may vary from 10 to 30 carbons and are a component of lipids. Fatty acids such as saturated fatty acids and unsaturated fatty acids are found in marine fishes, microalgae, seaweeds, fish oil, algae oil and eggs. Omega-3 PUFAs have been broadly studied in clinical and pathological conditions. The consumption of omega-3-PUFAs and nutraceutical foods has been correlated with human health benefits. Omega-3 fatty acids have many clinical benefits, including reducing the risk of tumor growth and metastasis. The highest level of omega-3 fatty acids can alter eicosanoid synthesis and have anti-catabolic effects. The supplementation of these essential fatty acids, eicosapentaenoic acids (EPA), docosahexaenoic acid (DHA), protects against colon and breast cancer [46]. Hence, it controls weight loss in cancer patients, regulates cytokine production and stabilizes the energy metabolism. Several clinical studies evaluated high fat and low carbohydrate fish oil supplement as a potential therapeutic for colon cancer. Omega-3 fatty acid contains in fish oil supplements, stimulates the immune response and enhances apoptosis in cancer cells [47]. Fusano et al. [48] suggested that n-3 fatty acids have antitumor effects during the initiation stages of colon carcinoma. The omega-3 fatty acids reduce the proliferation of early-stage colonic cancers, which may reduce the progression colorectal polyps and may help protect high-risk individuals from colon cancer.

### **Honey (eugenol):**

Eugenol is a natural compound which is derived from honey and is present in some plant extracts including clove oil, cinnamon, Flos Magnolia, citrus and balm. Eugenol exhibited novel medical applications for curing various chronic diseases. It promotes apoptosis in colon cancer cells [49]. Eugenol is a potential natural drug against colon cancer. Eugenol stimulates cell division in sub-G1 phase inducing apoptosis in regular time-dependent manner. It acts as a transducer of an apoptosis signal to control the production of non-protein thiols and matrix metallo-proteins (MMP). Eugenol-treated colon cancer cells demonstrated increased p53 activation and proline rich acidic protein (PRAP) cleavage [50].

### **Vitamins for colon cancer prevention:**

Vitamins are playing essential role in cancer prevention and treatment. Folic acid plays a major role in DNA methylation and DNA synthesis. It conjugates with vitamins B6 and B12 in the single carbon methyl cycle. Vitamin B complex treatment was initiated to reduce the risk of colon, rectal and breast cancer [51]. Similarly, vitamin D receptor molecules are highly expressed in colon cancer cells, and may control the abnormal metastasis and regulate the cell death mechanism in colon cells [52]. Table illustrates the different dietary nutraceuticals tested in colon cancer preventive medicine.

### **Marine nutraceuticals and their derivatives for colon cancer**

The marine environment contains an extreme diversity of micro- and macro-organisms. Marine organisms contain structurally diverse bioactive compounds including many that are included in food and health care products. Marine organisms produce novel and pharmacological compounds with fewer adverse effects. Marine-derived bioactive compounds are of current interest to cure



several ailments including colon cancers. However, researchers are focusing more on secondary metabolites isolated from marine and other natural sources. Recently natural product research has reported that from 1981 to 2012, 45% of new drugs and 80% drugs approved for anticancer agents were derived from natural products [53].

### **Acetylapoaranotin**

Acetylapoaranotin is a diketopiperazine disulfide that was isolated from marine *Aspergillus* sp. The acetylapoaranotin chemical structure contains disulfide bridges, which are responsible for the molecule's cytotoxicity. The natural acetylapoaranotin compound can induce apoptosis in human colon cancer cells (HCT116) as confirmed by different apoptotic assays such as annexin-V/PI staining and PARP, caspase-3, -8, -9, and Bax cleavage. This compound also significantly inhibits tumor growth in vivo. Choi and researchers [54] are evaluating the molecular role of diketopiperazine disulfides in apoptosis of the HCT 116 colon cancer cell line. Acetylapoaranotin has promising activity to regulate the Bcl-2 family of proteins and the proapoptotic protein Bax. Treatment of the cancer cell line HCT 116 with different concentrations of diketopiperazine disulfides was shown to initiate the caspase 8 activation in intrinsic and extrinsic pathways. Various types of marine-derived compounds have numerous biomedical applications such as the neuroprotective properties of seaweeds, chitosan for weight management and dentistry. Also marine plants and animals have a rich source of novel compounds with promising uses in the nutraceutical, medicinal and commercial food industries. The marine-based nutraceuticals such as glucon, sulphated polysaccharides, peptides and fatty acid immunomodulators have great application in the pharmacological and commercial industries. Seaweed-derived peptides and proteins can modulate the intestinal epithelium cell permeability and consequently enhance the intestinal absorption of macromolecules through the energetic pathways [55].

### **Astaxanthin**

Astaxanthin is one of the carotenoid classes of secondary metabolites, and is abundantly produced by *Haematococcus pluvialis*, crab and marine animals. The highest content of astaxanthin was found in *H. pluvialis*, a single-celled green algae. Its chemical name is 3, 3'-dihydroxy- $\beta$ ,  $\beta$ -carotene-4,4'-dione. Astaxanthin (ASTX) has diverse biological applications to control colon ulcers, inflammation, cancer, and neurological disorders. Astaxanthin is also used as a food supplement to enhance the optimal health for humans [56]. Treatment of a colon cancer mouse model with astaxanthin was shown to generate normal expression of NF- $\kappa$ B, MMP9, IL-6, TNF $\alpha$ , COX-2, and inhibit proliferation and induce apoptosis. Also, dietary ASTX significantly suppressed the formation of colonic mucosal ulcers and dysplastic crypts in an animal model. NF- $\kappa$ B is a transcription factor which participates in a wide range of cellular roles and cancer pathways. NF- $\kappa$ B factors are critically involved in various signaling mechanisms, particularly which regulate posttranscriptional function. Astaxanthin has specific functional groups to regulate the NF- $\kappa$ B proteins [57]. 1, 2-dimethylhydrazine (DMH)- induced colon carcinogenesis was markedly reduced by astaxanthin. It has a good chemopreventive effect on lipid peroxidation, antioxidant status, the total number of aberrant crypt foci (ACF), and cell proliferation, and eventually reduced the histological lesions in a rat model.

### **Siphonaxanthin**

Siphonaxanthin is isolated from the marine green alga *Codium fragile* and remarkably suppresses cell viability, and induces apoptosis in human leukemia and colon cells. Siphonaxanthin has significant antiangiogenic activity by suppressing endothelial cell proliferation and HUVEC tube formation. Although siphonaxanthin had a strong inhibitory effect on micro-vessel formation in an angiogenic model, it might not act through signal transduction by VEGF receptor-2. Siphonaxanthin induces apoptosis in HL- 60 cells through caspase-3 activation, which has been associated with the

enhancement of GADD45 $\alpha$  and DR5 expression levels as well as the suppression of Bcl-2 expression. GADD45 $\alpha$  is an important apoptosis regulator that induces cell cycle arrest and DR5 death [58, 59]. receptor.

### **Curcumin**

Curcumin diffuses through cell membranes into the endoplasmic reticulum, mitochondria, and nucleus, where it exerts actions, as an antioxidant property. Therefore, its use has been advocated for chemopreventive, antimetastatic, and anti-angiogenic purposes. We conducted a literature review to summarize studies investigating the relationship between curcumin and colorectal cancer (CRC). In vitro studies, performed on human colon cancer cell lines, showed that curcumin inhibited cellular growth through cycle arrest at the G2/M and G1 phases, as well as stimulated apoptosis by interacting with multiple molecular targets. In vivo studies have been performed in inflammatory and genetic CRC animal models with a chemopreventive effect. To improve curcumin bioavailability, it has been associated with small particles that increase its absorption when orally administered with excellent results on both inflammation and carcinogenesis. Curcumin has been used, moreover, as a component of dietetic formulations for CRC chemoprevention. These combinations showed in vitro and in vivo anticarcinogenic properties in inflammation-related and genetic CRC. A synergic effect was suggested using an individual constituent dosage, which was lower than that experimentally used “in vivo” for single components. In conclusion, curcumin falls within the category of plant origin substances able to prevent CRC in animals. This property offers promising expectations in humans [60].

### **Alkaloids and Colon Cancer**

Extracts and alkaloids isolated from plants have shown a role in the suppression of oncogenesis. Alkaloids have demonstrated an effect on the regulation of various mechanistic pathways involved in proliferation, cell cycle, and metastasis, thereby attracting considerable attention. From a clinical perspective, vincristine and vinblastine have historical importance as anticancer agents and are clinically used in the treatment of acute lymphoblastic leukemia [61]. Antitumor drugs, such as vincristine, vinblastine, and paclitaxel, which are being utilized in clinical practice, can exist naturally. Additionally, vincristine or vinblastine treatment has been shown to limit cancer growth in the majority of patients with complicated hemangiomas. These botanicals act through multiple mechanisms and have shown efficacy in breast, ovarian, non-small cell lung, and prostate cancers [62- 64]. Berberine (BBR), a fully natural isoquinoline alkaloid obtained from various botanical groupings, has recently attracted attention. Berberine has been shown to be beneficial for immunotherapy by acting as a dopamine receptor antagonist and suppressing the release of Interferon gamma (IFN- $\gamma$ ), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), Interleukin-1 beta (IL-1 $\beta$ ) and Interleukin-6 (IL-6) from LPS-activated cells. BBR has been shown to inhibit tumor proliferation, to induce autophagy and apoptosis, and to suppress metastasis and angiogenesis [65].

### **Use of Nutraceuticals with Immune Checkpoint Inhibitors**

Considering the remarkable effects of prebiotic molecules and probiotic species on the mucosal immune landscape, it can certainly be inferred that nutraceuticals may modulate the effect of immune-targeted treatments in colon cancer. This seems even more possible given our increased understanding of the role of the microbiota in the efficacy of checkpoint inhibitors. Indeed, the addition of nutraceuticals to immune checkpoint inhibitors have been promising, both in offsetting the drugs' intestinal side effects as well as augmenting the drugs' clinical efficacy (Bhatt et al., 2017). Antibodies against CTLA-4 have evolved as novel methods in cancer immunotherapy. Tumors of several cancer models, including colon cancer, did not respond to Ipilimumab (an anti-

CTLA-4 antibody) if given in antibiotic-treated or germ-free mice. This resistance to Ipilimumab can be overcome by administration of *B. fragilis*, suggesting a practical role of microbiota in cancer immunotherapy in general and CRC in particular. On the other hand, anti CTLA-4 administration can be associated with severe colonic inflammation and colitis in clinical practice; Patients that are more resistant to Ipilimumab-induced colitis are found to have increased *Bacteroidetes spp.* (Dubin et al., 2016), which suggests a potential implication of microbial targeted interventions in modulating the side effects from immunotherapy. Microbiota effects were also observed for other types of immunotherapy such as anti-PD-L1 therapy (Sivan et al., 2015). It was observed in mice that an increase in a commonly-applied genus of bacteria could reinforce the cytotoxic immune response encouraged by the immunotherapy (Sivan et al., 2015). Besides aid in the encouraged immune response, it can be speculated that their effects on cell death and metastasis would greatly increase the number of cancer cells killed which can further prevent spread of these cancer cells (Algam-Dimantov et al., 2013; Gamallat et al., 2016). Therefore, nutraceuticals show great promise in their use with immune checkpoint inhibitors for the treatment of colon cancer cases.

### Future Perspective

The finger prints of phytochemical compounds, especially nutraceuticals, are well established for the treatment of colon cancer. Dietary phytochemicals are widely used as pharmaceuticals beneficial for human health and other commercial products. However, the mechanisms of action of nutritional databases need further development and better molecular identification in colon cancer treatment. Also the in vivo data for many potent dietary phytochemicals activities is not yet analyzed. Nevertheless, the scientific community will be focused on naturally occurring nutraceuticals and their application in colon cancer therapeutics in detail. The natural diet contains diverse secondary metabolites such as flavonoids, steroids, sulphur-containing compounds, alkaloids, saponins, phenolic acids, vitamins, minerals and other antioxidant enzymes. These nutraceutical compounds may increase the protection from different factors such as red meat, high alcohol consumption and other drugs. Research has proven that the high intake of nutraceuticals is beneficial in the control of colon cancer generation. Finally, it should be recognized that single or clustered dietary nutraceuticals molecules are contributing to therapeutic action and will be important for future assessment.

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