Chapter 11
Phytoestrogens as a Natural Source for the Possible Colon Cancer Treatment

Suresh Challa, Rajanna Ajumeera, and Naresh Venna

Abstract Phytoestrogens (PEs) are naturally available bioactive compounds widely available in a spectrum of sources such as plant foods and are said to exhibit estrogen-like, antioxidant, and anticancer properties. There are wide range of PE-containing sources which are usually consumed by humans such as isoflavones (IF), coumestans, and lignans. Many of the fruits, vegetables, and whole grains are known to contain PE. For example, soybeans mainly contain IF, and flaxseeds mostly contain lignans, while clover, alfalfa, and soybean sprouts are rich in coumestans. There are many factors which affect the way these compounds act in a cell type such as estrogen receptor (ER)-α and ER-β levels and the amount of co-activators and corepressors present. The proposed mechanism by which these PEs work is by exerting their antioxidant effects through the inhibition of tyrosine kinase as well as DNA topoisomerase activities and also by suppressing the process of angiogenesis. Findings from molecular, cellular, and animal studies suggest that PE may potentially confer health benefits related to colon cancer (CC) pathology. High incidence of CC might be resulted with the intake of high-calorie diet including consumption of saturated fat and practicing sedentary lifestyle, whereas PEs from fiber-rich food could serve as prophylactics. The aim of this chapter is to elucidate the mechanistic approaches of different plant-based estrogens in combating colon cancer and their possible beneficial and clinical effects and therapeutic implications.

Keywords Benefits · Colon cancer · Consumption · Isoflavones · Phytoestrogens

11.1 Introduction

Developing countries are witnessing colon cancer as the most predominant type of cancer with roughly 2.2 million people suffering from the disease worldwide (Arnold et al. 2017). A fundamental reason could be that the changes in the food

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consumption pattern lead to colon cancer development, especially in the Western world. Phytoestrogens are among the most widely studied dietary bioactive components which have potential curative properties and can reduce the growing prospects of heart diseases and bone-related disorders as well as alleviate the menopausal symptoms and some hormonal cancers. Till today, several studies have shown that high consumption of PEs results in low incidence of developing tumors in the prostate, ovary, and colon (Hwang and Choi 2015; Gupta et al. 2016; Rietjens et al. 2017; Hussain and Green 2017). Parkin et al. (2002) have shown that the higher incidence of cancer in Western population compared to Asian population might be because of low dietary intake of PE which plays a protective role against cancer possibly by lowering down the unconjugated sex hormones in the circulation. Among sex hormones, estrogens regulate the development of colon cancers through its receptors, particularly ER-α and ER-β. Several studies have indicated the fact that PE structure is similar to mammalian hormone estrogen and, metabolically, they act as estrogen agonist and antagonist. Binding of PE to ERs and subsequent interaction with process of sex steroid biosynthesis result in reducing the cancer risk (Hwang and Choi 2015; George et al. 2017; Amawi et al. 2017). In addition, PEs not only show hormonal activity, but they also show some important non-hormonal activities that are involved in cancer prevention. The other mechanisms involved in differentiation of colon cancer are by inhibiting the activity of kinases and obliterating the process of tumor angiogenesis as well as DNA topoisomerase 1, which are involved in induction of cancer cell apoptosis (Shafiee et al. 2016; Rietjens et al. 2017). Colon cancer incidence rate is higher in Western population when compared to Asian population because of food habits. Individual's age and sex are also important factors in the increased incidence of colon cancer. However, population with the age group of 50 and above has shown greater risk of colon cancer incidence, and mortality rate appears to be greater in male population when compared with women. Dietary habits also strongly influence the risk of colon cancer. Few reports suggest that people consuming high-fat diet and red and processed meat and not taking proper amount of fruits and vegetables are having a higher risk of colon cancer. Moreover, several lifestyle factors such as alcohol consumption, lack of physical activity, and metabolic diseases also influence the incidence rate of colon cancer. In addition, environmental factors are also responsible for the cause of colon cancer such as migration of people from one type of climate region to another region (Janout and Kollarova 2001; de Jong et al. 2005; Larsson and Wolk 2006; Wiseman 2008; Haggar and Boushey 2009). Tumor occurs over an extended period in a multistage process in humans and is dependent on several factors. Modifications in both genetic and an epigenetic factor appear to be responsible for conversion of normal to cancerous cells. Malignant cells vary from normal cells by many properties, such as continuous cell proliferation, resistance to growth inhibition, and resistance to apoptosis, and supporting angiogenesis and metastasis. These mechanisms also involve physiological changes and alteration of signal transduction pathways (Gupta et al. 2010).

Cancer of both colon and rectum is often considered as a colorectal cancer, which affects the lower part of the digestive system. Several studies have shown that the

risk of colon cancer will be enhanced by adenomas and polyps. In most cases, colon cancer started as small noncancerous clusters of cells called adenomatous polyps; in some of the cases, the polyps are converted to colon cancer. Adenomas are categorized into two types, conventional adenomas and sessile serrated polyps. In most of the cases, these two types of adenomas are responsible for colorectal cancer (Strum 2016). Predominantly adenomas are seen in distal colon in the age group of below 60 years, and above this age they are mostly found in the proximal colon (Zauber et al. 2012). The microsatellite instability pathway and chromosomal instability pathways are responsible for the conversion of adenomas into carcinoma. In both pathways, genes affected by somatic mutation are responsible for the most diverse cancers (Lin et al. 2003; Leary et al. 2008; Nishihara et al. 2013; Strum 2016). Prevalence of colon cancer is sporadic in majority of the cases, and 2–6% cases are hereditary disease due to mutation of autosomal dominant genes. Most commonly mutated tumor suppressor genes (TSGs) are APC and TP53, and most commonly mutated oncogenes are BRAF, KRAS, and P13KCA genes. There are two types of inherited conditions found in colorectal cancer such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. Mutation of mismatched repair genes and tumor suppressor genes is responsible for familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC or lynch syndrome), respectively, and mutation of TSG-APC might lead to familial adenomatous polyposis. The MLH1 and MLH2 genes function as DNA mismatch repair pathway; mutation of these two genes is responsible for HNPCC (Papadopoulos et al. 1994; Smith et al. 2002; Wang et al. 2004; Pampaloni et al. 2013; Crockett et al. 2015; Strum 2016). The aim of this chapter is to elucidate the mechanistic approaches of different plant-based estrogens in combating colon cancer, their possible beneficial and clinical effects and therapeutic implications.

11.2 Mechanism of Carcinogenesis

Three different mechanisms are responsible for colorectal cancer: (1) chromosomal instability (CIN), (2) microsatellite instability (MSI), and (3) CpG island methylation (CIM). One or combination of these three pathways is involved in the development of colorectal cancer (Fig. 11.1). CIN is involved in the mutations of adenomatous polyposis coli (APC), followed by mutation of TSGs and tumor oncogenes. Sixty to seventy percent of sporadic colorectal cancer cases arise by chromosomal instability. This pathway is associated with aneuploidy, which is improper segregation of chromosomes in mitotic divisions. Defect in checkpoints in mitotic divisions is responsible for chromosome mis-segregation, and this condition leads to aneuploidy. Mutation of the following genes such as mitotic arrest deficient (Mad1 as well as Mad2); budding uninhibited by benzimidazoles 1 (BUB1); hZw10, hZwilch/FLJ10036, and hROD/KNTC genes; and kinesin family member 11 (KIF11) can result in chromosomal instability. Several other mechanisms are also driven to chromosomal instability: abnormal centromere number and function,

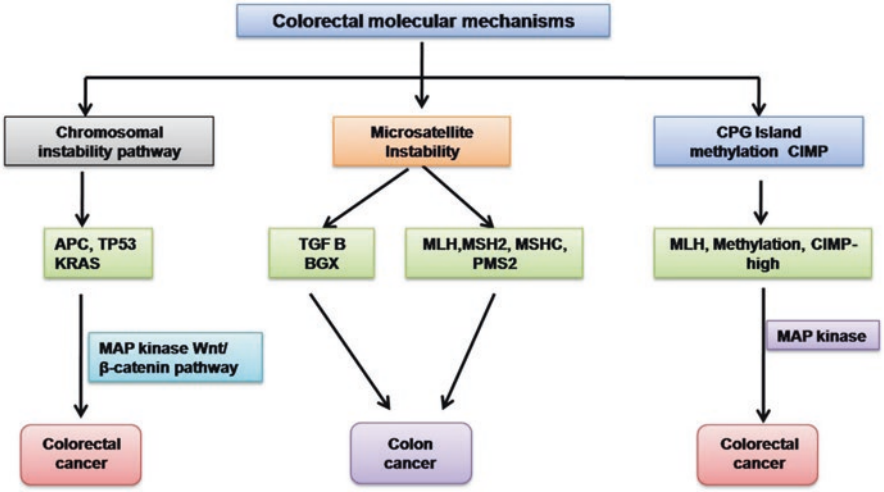

Fig. 11.1 Molecular mechanism of colorectal carcinogenesis

telomere dysfunction, loss of heterozygosity, defect in DNA damage response, and mutation of proto-oncogenes and TSGs (KRAC, APC, and TP53). In colorectal carcinogenesis, the earliest genetic event is Wnt pathway activation. The tumor suppressor gene APC regulates the beta-catenin/Tcf pathway. Mutation of APC gene allows accumulation of beta-catenin in cytoplasm. This beta-catenin binds to DNA-binding protein transcription factor and moves to the nucleus, followed by transcription of genes containing TCF-DNA-binding sites which regulates proliferation, migration, and adhesion of colorectal cells (Smith et al. 2002; Wang et al. 2004; Roper and Hung 2013; Colussi et al. 2013; Tariq and Ghias 2016).

Microsatellite instability pathway is responsible for 12–17% of all colorectal carcinogenesis with only 3% associated with hereditary nonpolyposis colorectal carcinogenesis and remaining are sporadic cases driven by the hypermethylation of the MLH1 gene. Microsatellite is driven by inactivating the mutation of DNA mismatch repair genes. The main function is correcting DNA replication error; DNA mismatch repair system has important components including hPMS1, hPMS1, hMLH1, hMSH2, hMSH3, and hMSH6. Another target gene in the microsatellite colorectal carcinogenesis pathway is the TGF-β receptor 2 (TGF-βR2). TGF-β is a negative regulator of proliferation in colon epithelial cells. Mutation of Smad2 and Smad4 genes regulates the TGF-β pathway that leads to MSI colorectal carcinogenesis. Another mutational target gene of microsatellite instability colorectal carcinogenesis is active in type 2 receptors (ACVR2) and tumor suppressor gene BAX. ACVR2 executes an important function in differentiation and growth suppression by phosphorylating Smad2 and Smad3 proteins. Several studies have shown ACVR2 mutation to frequently occur with TGF-β2 mutations. Tumor suppressor gene BAX regulated the intrinsic apoptosis mechanism. Fifty percent of colorectal carcinogenesis cases are caused by homologous frameshift mutation of

BAX gene and cells escaping from the intrinsic apoptosis mechanism. CpG island methylation phenotype (CIMP), methylation of DNA at the cytosine base of CpG islands are done by DNA methyltransferase enzyme. An initial CIMP tumor occurrence could be a quick shift in the BARF proto-oncogenes, and usual colonic epithelial cell apoptosis is prevented. CpG island methylation takes place in the mismatch repair gene MLH1, and subsequently its transcriptional inactivation leads to the formation of malignant tumor (Takayama et al. 2006; Zhang et al. 2010; Roper and Hung 2013; Colussi et al. 2013; Tariq and Ghias 2016).

11.3 Metastasis

Maximum carcinoma-related fatalities are due to complication in correlation with metastasis. Cancer that spread from tissues to organs from the site of origin to a distant target within the body ends up in generating metastasis. Tumor formation requires multifarious cancer cells, and from these everyday at least 10% of the cells infiltrate into the circulation. This particular event ends up in replacing normal cells with cancerous tumor cells in different kinds of body tissues. Predominantly, metastasis occurs in the late phase in the development of carcinoma; henceforth surgery is a good option to treat the small tumor that is being formed in the initial stages (Guillerey and Smyth 2015). This metastatic process is termed as a battery of independent, rate-limiting, and continuous process. The brief events that take place during metastasis process are as follows.

11.3.1 Angiogenesis

It is the process of fabrication of fresh blood capillaries, and it involves important events like migration, growth, and proliferation of the cells that are endothelial in nature. The cells are lined up inside the wall of the blood vessels (Folkman 2002).

11.3.2 Intravasation

It is the process of cancer cell invasion through basal membrane in the circulation either in blood or lymphatic system. Critically during this process, the cancerous cells break out from their primary sites.

11.3.3 Survival in Circulation

Largest number of circulation cancer cells happens to die within 24 h by different processes such as cytotoxicity or by lysis by NK cells. After intravasation, tumor cells normally will be protected by platelets and platelet-derived microparticles (Sakurai and Kudo 2011).

11.3.4 Extravasation

It is known that tumor cells exudate through venules and then migrate to arterioles where the oxygenation for the tissue is more.

11.3.5 Secondary Tumor Formation

Tumor cells often spill into the circulation possibly through the process of apoptosis and get exterminated by immune cells (Hedley and Chambers 2009). Ultimately to become a secondary tumor, cancerous cells should divide and have to undergo angiogenesis. Some of the studies indicates that early angiogenic stages of metastatic growth in bone-marrow-derived EPC, while few suggest that co-option of normal vessels is a mechanism for metastasis vascularization (Folkman 2002; Guillerey and Smyth 2015; Bielenberg and Zetter 2015).

11.4 Treatment of Colon Cancer

Treatment for cancer varies from one individual to another, and treatment options and recommendations depend on several factors. The major factors include stage and type of cancer, age of the individual, and health condition of the patient. The most common treatment options are surgery, radiation therapy, chemotherapy, and targeted therapy.

11.4.1 Surgery

Surgery is the most common treatment for early stages of colorectal cancer. It involves removal of the tumor and small amount of surrounding healthy tissue and is often called surgical resection. Surgical options for colorectal cancer are

polypectomy and colectomy. When the tumor is removed as part of the polyps, then it is called polypectomy. Removal of complete colon or part of the colon and surrounding lymph nodes during surgery is called colectomy. A complete removal of the colon is called total colectomy, and if only a part of the colon is removed, then it is called partial colectomy. In general, the side effect of surgery is pain and tenderness in the area of operation.

11.4.2 Radiation Therapy

Radiation therapy uses high-energy rays (X-rays or gamma rays) or charged particles to kill the cancer cells. Sometimes the tumor cannot be completely removed by surgery; hence radiation therapy can be used to treat the cancer cells. Radiation therapy in combination with chemotherapy acts effectively on few colorectal cancers. These two treatments are together referred to as chemoradiation therapy. Treatments of colorectal cancers involve the use of different types of radiation therapy which are listed below.

11.4.2.1 External Beam Radiation Therapy

External beam radiation therapy which is used to treat colorectal cancers uses X-rays coming from outside of the body through a machine and is delivered to where the tumor is located.

11.4.2.2 Internal Radiation Therapy

Brachytherapy is most commonly used for the treatment of colorectal cancer. The convenience of this treatment is that the radiation doesn't cross the skin and other tissues to cure the tumor; henceforth the side effects are very less.

11.4.2.3 Stereotactic Radiation Therapy

Stereotactic radiation therapy uses radiation at a very high dose. This is also a type of external beam radiation therapy that is mainly used if a tumor is in metastasis stage. The advantage of this technique can help avoid removing parts of the tissues that might be removed during surgery. In general, the possible side effects from radiation therapy are skin irritation, nausea, fatigue, stomach upset, painful bowel movement, sexual problems, and infertility in both male and female.

Table 11.1 FDA-approved drugs for chemotherapy

Drug name	Mechanism of action
Fluorouracil (5-FU)	Disrupts DNA and RNA synthesis
	Inhibits the enzyme thymidylate synthase – key enzyme in the creation of the DNA nucleotide dTMP – and impairs DNA synthesis in the S phase of the cellular replication cycle
	Creates incorrect nucleotides which are incorporated into DNA and interferes with normal protein production leading to cell death
Capecitabine (Xeloda)	Capecitabine inhibits de novo synthesis of DNA by inhibiting thymidylate synthase. It is a key enzyme for the synthesis of thymidine monophosphate
	Capecitabine is metabolized to 5-fluorouracil by thymidine phosphorylase; this enzyme's expression is more in cancer cells compared to normal cells
Irinotecan (Camptor)	Disrupts DNA replication and transcription
	Inhibits DNA topoisomerase I, relaxes super-coiled double-stranded DNA, and prevents DNA religation
Oxaliplatin (Eloxatin)	Induces apoptotic cell death
	Causes inter- and intra-strand DNA cross-links and halts replication and transcription
Trifluridine	Trifluridine is a standard antiproliferative agent with two types of mechanisms of action; it inhibits thymidylate synthase (TS) and is also integrated into DNA

11.4.3 Chemotherapy

Chemotherapy uses one or more anticancer drugs to kill the cancer cells. This treatment uses single or combination of different drugs to treat the individual at the same time. Several research studies have shown that combination of chemotherapy and target therapies is increasing the survival rate of cancer patients. In systematic chemotherapy, drugs are directly injected into the veins or given in the form of pills or capsules. The given drug is distributed all over body through the bloodstream. In adjuvant chemotherapy, treatment is given to the patient after all the visible and known tumors have been removed by surgery and will be used to prevent the reoccurrence of cancer. Neoadjuvant chemotherapy is the administration of drugs prior to the surgery or radiation therapy. The main approach of this chemotherapy is reduction in size of the tumor and inhibition of spreading of tumor. Frequently used FDA-approved chemotherapy drugs for treating colorectal cancer (Table 11.1) include fluorouracil (5-FU), capecitabine (Xeloda), irinotecan (Camptor), oxaliplatin (Eloxatin), and trifluridine (André et al. 2004; Ciombor et al. 2015; Hammond et al. 2016). Chemotherapy effects depend on type and dose of drugs advised and period of consumption. Loss of hair, anorexia, bleeding, fatigue, mouth ulcers, and nausea are regular adverse effects of chemo drugs, diarrhea being the most common. Among FDA-approved chemo drugs, oxaliplatin causes nerve damage with tingling sensation and numbness in hands and feet, skin rashes, and trouble in

Table 11.2 FDA-approved target therapy drugs

Drug name	Mechanism of action
Regorafenib	Inhibits the vascularization and growth
Bevacizumab	Reduces the formation of new vasculature
	Induces local hypoxia and blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A)
Aflibercept	Regression of tumor vasculature and new vascular growth
	Binds to circulating VEGFs and inhibits the activity of the vascular endothelial growth factor subtypes VEGF-A and VEGF-B, as well as placental growth factor (PGF)
Cetuximab	Inhibits cell growth and survival
	Binds to the external domain of the EGFR – receptor is internalized and degraded without activation or phosphorylation
	Induces antibody-mediated cytotoxicity
	Downregulates the VEGF expression
Panitumumab	Panitumumab selectively binds to epidermal growth factor receptor (EGFR) and induces internalization of EGFR
	Induces apoptosis
	Inhibits cell proliferation, decreases the expression of pro-inflammatory cytokines and VEGF

breathing being the major symptoms, and capecitabine or 5-FU (when given as an infusion) when used for hand and foot treatment causes redness in hands and feet initially and ends up in pain and sensitivity.

11.4.4 Target Therapy

Target therapy is different from the conventional chemotherapy, as in this treatment drugs are targeted to specific genes, proteins, or tissue environments that support tumor growth and survival. Target therapy mainly involves two kinds of drugs to treat cancer; monoclonal antibodies inhibit specific target outside the cancer cells or the target of surrounding environment of cancer cells and are administered intravenously (IV). Monoclonal antibodies can also be delivered through toxic substance and directly sent to cancer cells. Next to monoclonal antibodies, small molecular drugs are targeted to inhibit the process that supports cancer cell metastasis and growth. Generally these drugs will be taken as pills or capsules orally. There are two main types of target therapies for colorectal cancer (Table 11.2).

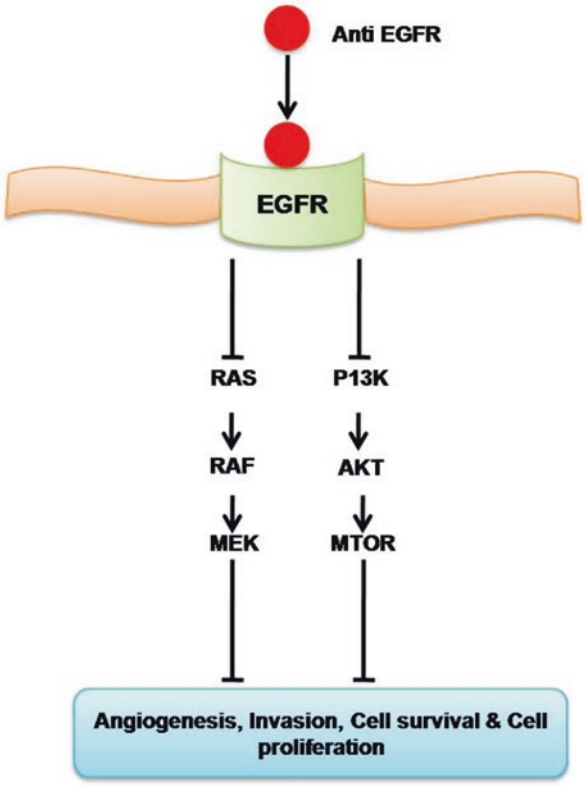

Fig. 11.2 Possible mechanism of anti-EGFR drugs and its targets

11.4.4.1 Anti-angiogenesis Therapy (Inhibition of VEGF)

Anti-angiogenesis therapy uses drugs to target and inhibit vascular endothelial growth factor (VEGF) which is mainly involved in tumor angiogenesis. Commonly used anti-angiogenesis therapy drugs are bevacizumab (Avastin), regorafenib (Stivarga), ziv-aflibercept (Zaltrap), and ramucirumab (Cyramza).

11.4.4.2 Epidermal Growth Factor Receptor (EGFR) Inhibitors

EGFR is overexpressed on the surface of cancerous cells and is mainly involved in the progression of tumor. The possible mechanisms of EGFR are that epidermal growth factor receptor ligands (EGFRL) bind the extracellular domain of EGFR, initiate receptor activation, and stimulate downstream signaling pathways such as PI3K/AKT and RAS/RAF/MAPK pathways. These signaling pathways are involved in cell growth, proliferation, angiogenesis, and metastasis (Fig. 11.2). Cetuximab or panitumumab drugs (anti-EGFR drugs) block ligand binding to EGFR, thus inhibiting EGFR downstream signaling pathways. Cetuximab (Erbitux) and panitumumab

(Vectibix) are the most commonly used drugs that act as inhibitors of epidermal growth factor receptors and hamper the tumor progression (André et al. 2004; Ciombor et al. 2015; Hammond et al. 2016).

11.4.4.3 Possible Side Effects of Drugs of Ziv-Aflibercept and Bevacizumab

Lethargy, high blood pressure, bleeding, low white blood cell counts, mouth sores, food aversions, and diarrhea are the most common side effects of these drugs, while blood clots, severe bleeding, holes forming in the colon (called *perforations*), kidney problems, allergic reactions, and slow wound healing are rare but possible serious adverse effects.

11.4.4.4 Possible Side Effects of Drugs Cetuximab (Erbitux), Panitumumab (Vectibix), and Regorafenib (Stivarga)

Regular side effects of these drugs include skin problems which can sometimes lead to infections. Panitumumab causes serious skin problems that lead to skin peeling. Other side effects include fever and diarrhea and allergic reaction during the infusion, which could cause low blood pressure and breathing problems. Regorafenib causes fatigue, loss of appetite, hand-foot syndrome, diarrhea, high blood pressure, weight loss, and abdominal pain. Severe bleeding and perforations in the stomach or intestines could be categorized as more serious side effects but are found to be less common.

11.5 Lifestyle, Nutrition, and Cancer

Lifestyle of an individual is responsible for nearly 90–95% incidence of all cancers, and the remaining 5–10% is associated with improper function of genes. Many epidemiological studies suggest that proper nutritious diet could reduce cancer deaths by up to 35%, and certain cancers could be totally avoided by up to 80–90% by consuming appropriate diet. Many plant-derived dietary compounds are known for their multi-targeting activities and, hence, referred as nutraceuticals (nutrition and pharmaceutical). Nutraceuticals are defined as compound considered being a food or part of the food that protect against pathological conditions and provide health benefits. These are biologically active compounds and can be used to target tumor cell development processes at various steps (Gupta et al. 2010; Pampaloni et al. 2013). Several studies at epidemiological level have shown tumor incidence at many sites which is negatively correlated to consumption of fruits and vegetables. Certain foods including fruits and vegetables reduce the risk of colon cancer. Several case control studies lowered the incidence rate of cancer by increased uptake of

fiber-containing foods. In addition, studies have shown 40–50% significant decrease in colon cancer and 50% decrease in colorectal cancer with higher uptake of fiber-containing fruits and vegetables. Dietary fibers, antioxidants (e.g., β-carotene, vitamin C), and anticarcinogenic constituents (e.g., protease inhibitors, PE) in these vegetables, fruits, and grains might have a potential protective effect, reducing the tumor risk (Block et al. 1992; Howe et al. 1992; Pampaloni et al. 2013).

11.6 Phytoestrogens

Phytoestrogens belong to a diverse class of compounds structurally and functionally similar to mammalian hormone estrogen (17-estradiol). These compounds are available in greens, grains, fruits, and vegetables. Phytoestrogens have a diverse biological activity because they can act both as agonists showing similar activity of endogenous estrogens and antagonists by inhibiting the estrogenic activity of estrogen hormone. Similar to estrogen agonists, these phytoestrogens cause estrogen-like effects; as estrogen antagonists, these phytoestrogens are categorized into mainly three important groups; they are isoflavones, lignans, and coumestans. Other classes of phytoestrogens are anthraquinones, flavones, prenylflavonoids, chalcones, and saponins.

11.6.1 Isoflavones

These are the most important PEs found in legume, soya, peanuts, and clover. Naturally occurring isoflavones, namely, daidzein (4,7-dihydroxyisoflavone), genistein (4,5,7-trihydroxy isoflavones), formononetin, and biochanin A (Ososki and Kennelly 2003; Dixon 2004) (Fig. 11.3), show similar activity to mammalian estrogen hormone. Once mammals consume isoflavones, they are metabolized to daidzein and genistein in the gastrointestinal tract, and further, biochanin A and formononetin are metabolized, respectively, to genistein and daidzein (Kurzer and Xu 1997). Genistein is the most effective compound of all the isoflavones with anticancer and antioxidant properties (Hussain and Green 2017). Several studies have tested genistein and showed that cancer cells are inhibited under high concentration and proliferated in low concentration. However, there are some studies on PEs showing to have a very little effect as antioxidants; soymilk and supplementary soy isoflavones are protective in lipoprotein against oxidation and oxidative DNA damage in postmenopausal women. In humans glutathione peroxidase is the most important enzyme in antioxidation, and genistein helps in increasing of antioxidant enzymes (Anderson et al. 1999; Brownson et al. 2002; Li et al. 2012; Shafiee et al. 2016).

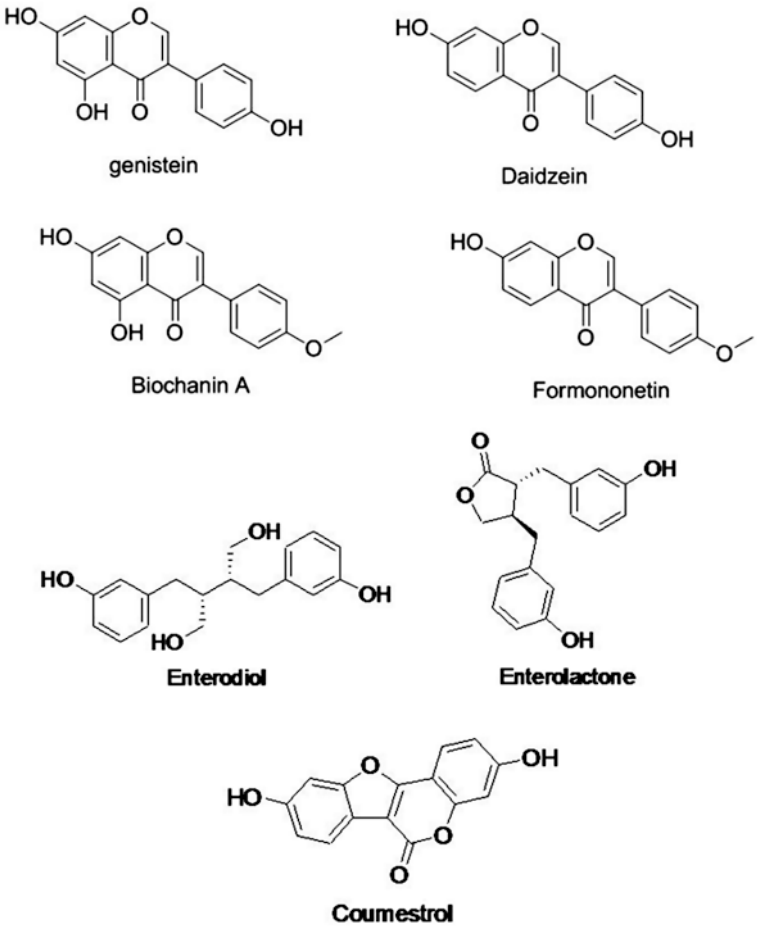

Fig. 11.3 Structures of isoflavones (genistein, daidzein, biochanin A, and formononetin), lignans (enterodiol and enterolactone), and coumestans (coumestrol)

11.6.2 Lignans

Lignans are another group of PE first recognized in plants. Lignans are later found in the biological fluids of mammals. It is a di-phenolic plant compound containing 2,3-dibenzyl butane structure formed by two cinnamic acid residues. Plant lignans' chemical structure differs from that of mammalian lignans as they lack the phenyl hydroxyl groups in aromatic ring at meta-position of the ring (Fig. 11.3). Lignans are highly available in rye bread, legumes, whole grains, vegetables, fruits, and oilseeds. High concentrations of lignans are found in the flaxseed. Seed coat, bran layer of seeds, and wooden portion of plants are sources of lignans with matairesinol

and secoisolariciresinol being the most well-known. These two plant lignans are converted into enterodiol and enterolactone, respectively, by bacterial action in the gut. In plants, lignans are conjugated with sugar moiety and are converted into unconjugated lignans through a series of metabolic reactions by gastric hydrochloric acid and anaerobic microbe-derived β-glycosidases. The administration of antibiotic- or microbe-free environment inhibits production and excretion of lignans. In mammals, once lignans are absorbed in the epithelial border of the intestine, they are re-conjugated in the liver by enzymes of UDP-glucuronosyltransferase and sulfotransferase. Intake of plant lignans has many health benefits; particularly, they reduce the risk of incidence of cancers. In addition, plant lignans also possess anticarcinogenic, antioxidant, antiproliferative, and apoptotic activities. As lignans are structurally similar to mammalian hormone β-estradiol, they influence the hormonal cancers via estrogen-mediated signal transduction pathways. Lignans are also involved in estrogen-independent pathways via insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor.

11.6.3 Coumestans

Coumestans are an important group of plant PE isolated from plants. The structure of coumestans is similar to mammalian hormone estrogen and shows estrogenic activity (Fig. 11.3). This group of PE is first reported by Bickoff and coworkers in 1957. Coumestans were first isolated from alfalfa or lucerne (*Medicago sativa*), ladino clover (*Trifolium repens*), and strawberry clover (*T. fragiferum*). Some of the plant coumestans were shown to have uterotropic activities. Coumestrol and 4-methxycoumestrol are important coumestans and shown to have estrogenic activity. These two coumestans are found in alfalfa and ladino clover. Important dietary sources of coumestans are sprouts of alfalfa and mung bean, and coumestans are especially higher in clover. It is showed that feeding of female rats with coumestrol resulted in suppression of estrous cycle and also negatively affected the sexual behavior of male offsprings. Coumestrol also regulates the metabolic effects and increases the lipid synthesis and glycogen catabolism (Kurzer and Xu 1997; Nogowski 1999; Ososki and Kennelly 2003; Dixon 2004).

11.7 Phytoestrogens and Colon Cancer Treatment

Colon cancer is considered to be an important disease, leading to majority of cancer deaths worldwide. In the last decade, there were numerous reports indicating that the increased prevalence of CRC could be because of alterations in lifestyle, improper nutrition, and environmental factors. The increased drug resistance and side effects resulting from the use of conventional radiotherapy, chemotherapy, and target therapy are a major problem in the treatment of colon cancer. Thus, it is

necessary to investigate effective anticancer drugs with low side effects for the treatment of colon cancer. Phytoestrogens, a diverse group of plant-derived polyphenolic bioactive compounds, are identical to estrogen based on their function and chemical structure. It is most commonly found in soy food. In humans, soy is a primary source of plant-derived proteins. A wide variety of biologically active chemical compounds are found in soy and soy food products which independently or combinedly contribute to health. Soy is rich in isoflavones, which has several health benefits. Isoflavones are structurally identical to estrogen molecule. PEs are considered to possess therapeutic properties and can prevent cancer. Reports indicate that exposure to PEs can inhibit the transition of G_2/M in tumor cells and can upregulate the cell cycle inhibitory molecule. PEs have several other mechanisms of action like EGF receptor inhibition, vascular endothelial growth factors, and TNFα. They can act as antioxidants, 3β- and 17β-hydroxysteroid dehydrogenase inhibitors, suppressors of angiogenesis, and inhibitors of aromatase mRNA expression and activity (Krazeisen et al. 2001; Li et al. 2005; Rice et al. 2006; Haggar and Boushey 2009; Virk-Baker et al. 2010; Barnes 2010; Hwang and Choi 2015).

Several epidemiological surveys indicate that a curtailed incidence of cancers is associated with hormones in Asia, where one can witness regular consumption of soy-based food. Thus, soybean consumption results in the reduction of cancer rates, showing the key role of PEs in cancer prevention, which are known to be highly potent antioxidants. However, soybeans are rich in trypsin inhibitors; they also contain other proteins like sphingolipids phosphatidylinositol, and saponins, which impart various advantages relating to health care. In summary, all three compounds present in soybean possess tumor-preventive properties in animal models (Birt et al. 2001; Pampaloni et al. 2013; Amawi et al. 2017). Several studies epidemiologically reported the association between reduced colorectal risk of cancer and soy food intake. Studies conducted in Asia and Hawaii also reported the same, but these findings need to be reassessed (Oba et al. 2007; Akhter et al. 2008; Yang et al. 2009; Budhathoki et al. 2011; Shin et al. 2015). Factors like gender differences contribute majorly to the incidence of CRC. The influence of female sex steroid hormones in women has a major role in lowering the death rate associated with colorectal cancer. Hormone therapy (combination of estrogen and progestin) on its pros side has protective role in development of CRC and is also known to reduce the risk of colon cancer to 32% in postmenopausal women, but on its cons side, it is associated with other risks especially showing higher incidence of heart diseases (Cotterchio et al. 2006; Barone et al. 2008; Nüssler et al. 2008; Pampaloni et al. 2013).

Some studies suggested that the PEs may show their protective role through the activation of estrogen receptor (ER)-β in the gastrointestinal tract, where ER-β is the predominant subtype of ER. Steroid hormone receptor members, namely, ERs and nuclear receptors, activate upon binding of the ligand forming a stable dimer resulting in the initiation of ER-specific response target gene transcription. The above dimer formation hampers in the absence of the ligand and initiates the binding of ER to shock protein. There are two main types of ERs, alpha (ER-α) and beta (ER-β). Estrogens exert their effects on target tissues by these ligand-activated transcription factors. They also show a varied distribution in tissues; for example, the

mammary glands and uterus mainly contain ER-α, while the endothelial cells, central nervous system, and colonic mucosa mainly contain ER-β (Pampaloni et al. 2013). Clinical studies have reported that CRC highly expresses ERs. Very low expression levels of ER-α and high expression levels of ER-β associated with the cellular differentiation and CRC stage were detected in normal or pathological colonic mucosa (adenoma and carcinoma). However, ER-β expression levels were less along the pathological mucosa, respectively. These findings showing the expression of ER-β protein getting lower in malignant tumors with respect to normal tissue have helped to develop a hypothesis that ER-β may act as a cancer suppressor, further preventing malignant transformation and uncontrolled proliferation (Glazier and Bowman 2001; Pampaloni et al. 2013; Williams et al. 2016).

11.7.1 Possible Mechanisms of Colon Cancer Prevention by PE Treatment

In addition to hormonal activities, some of the non-hormonal mechanisms of PE exist in treatment of tumor which include reduction in proliferation, changes in cell signaling, induction of detoxification enzymes, and induced cell cycle arrest, apoptosis, and anti-inflammatory and antioxidative properties. Wang et al. (1998) have demonstrated that dietary PE can have a new mode of action in CRC chemoprevention. In a study, six prominent PEs were examined in Colo205 cells for their potency to induce NADPH: quinone reductase (QR). However, there was no significant change in QR mRNA expression and activity upon daidzein or formononetin, enterolactone, and genistein treatment in a dose-dependent manner. However, effects of biochanin A and coumestrol QR expression were in moderation. Further, in this study, cell proliferation was most effectively inhibited by enterolactone (20%), followed by genistein (7%) and biochanin A (4%) (Wang et al. 1998; Lechner et al. 2005). Another interesting target for cancer chemoprevention is cyclooxygenase 2 (COX-2). Many studies have shown that colon tumor development involves COX-2 overexpression followed by prostaglandin overproduction. Among the PEs, however, genistein reportedly inhibits COX-2 expression in different cell types, such as gingival fibroblasts (Noguchi et al. 1996) and endothelial cells (Blanco et al. 1995). Suppressed COX-2 promoter activity is observed with increasing dose when Mutoh et al. (2000) examined the effects of genistein in DLD-1 human colon cancer cells that were transfected with the promoter sequence of the COX-2 gene in fusion with the β-galactosidase reporter gene. In addition, Mutoh et al. (2000) explained that the attributed effect was not only with mechanism involved in inhibition of tyrosine kinase but also suggested that the resorcin moiety in the genistein structure is critical since it is shared by other substances (Noguchi et al. 1996; Mutoh et al. 2000; Koehne and Dubois 2004; Lechner et al. 2005).

As per the literature, genistein is known for G2/M cell cycle arrest among various tumor cell lines. Among them, Park et al. (2001) for the first time studied colon

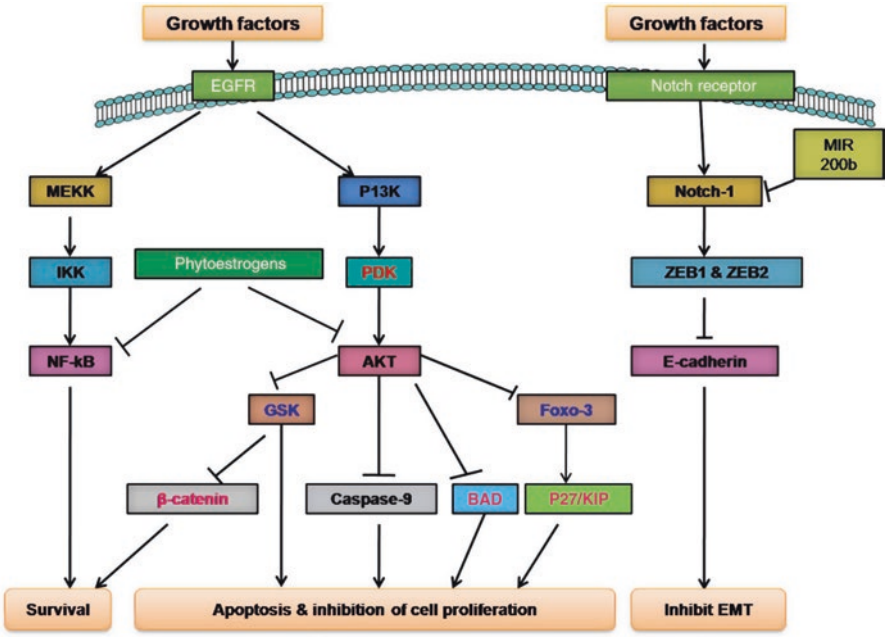

Fig. 11.4 Role of PE in signaling pathways, apoptosis, EMT, and cell proliferation

cancer cells and the effect of genistein in cell cycle progression. Genistein treatment showed increased expression and activation of p21waf1/cip1 protein and promoter reporter construct in Colo320 cells. In addition, authors have considered that genistein is a potential chemotherapeutic agent especially in combination with dexamethasone because of its correlation with G2/M arrest due to the activation of the cyclin-dependent kinase inhibitor p21waf1/cip1. A major component of soy products, genistein has been shown to have anticancer properties. In colon cancer cells, genistein has shown antiproliferative function via PI3K/Akt pathway by promoting FOXO3 activity and by inhibiting EGF-induced FOXO3 phosphorylation. Further, genistein increased FOXO3 activity by inhibiting EGF-induced FOXO3 disassociation from p53 (mut), increasing the expression of the p27kip1 cell cycle inhibitor, further inhibiting proliferation in colon cancer cells. These reports suggested that inactivation of FOXO3 is a key step in EGF-mediated proliferation (Fig. 11.4) (Sarkar and Li 2003; Qi et al. 2011a, b; Ganai and Farooqi 2015).

Further, there are reports of nearly 90% cancer-related deaths caused by tumor metastasis. The cancer cells possessing EMT properties lead to cancer metastasis by increasing the expression levels of motility-related proteins in the cell and increased migration and invasion to different parts of the body. Studies also indicate genistein targets various signaling pathways by specifically regulating the EMT process that results in the inhibition of cancer metastasis. Notch-1 signaling pathway contributes significantly to EMT phenomena by upregulating EMT markers such as ZEB1, ZEB2, Slug, and vimentin. Genistein treatment has been shown to reactivate miR-

200b, repressed by Notch-1 signaling, and hence suppress EMT process in AsPC-1 cells. Whenever miR-200b is reexpressed, reduced ZEB1 and vimentin expression, as well as enhanced E-cadherin expression, was observed thereby inhibiting the EMT process (Fig. 11.4) (Bao et al. 2011; Lee et al. 2016).

Lignan's role against colon tumor has been shown mostly by *in vitro* or *in vivo* studies. Enterodiol (EDL) and enterolactone (ENL) inhibited activation of c-fos in different breast and colon tumor cell lines. A new anticancer drug has been identified from *Phyllanthus urinaria*, a medicinal plant for cancer treatment. Drug is a substituted methylenedioxy lignin (7′-hydroxy-3′,4′,5,9,9′-pentamethoxy-3,4-methylenedioxy lignin), competent of activating caspases 3 and 8 and also c-myc in cancer cell lines through its ability to inhibit telomerase and bcl2. This compound may be serving as a chemotherapeutic drug after further evaluations (Giridharan et al. 2002; Webb and McCullough 2005). Lignans influence cancer via estrogen-mediated pathway, because of their structural similarity to 17-β estradiol. In addition, growth hormones, namely, insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF), in estrogen-dependent or estrogen-independent manner mediate the action of lignans. IGFs constitute a number of mitogenic factors which are anabolic in nature and help regulate growth and development along with various cellular processes. Also, few studies report IGF-1 showing effective mitogen characteristics involved in several cancers, like prostate, breast, and colon cancer. An investigation conducted in nude mice model with an ER-negative breast tumor showed a significant association with downregulation of IGF-1 and decrease in tumor growth and metastasis upon 10%-flaxseed diet. However in one study, estrogenic mechanisms had a little effect as observed in ER-negative experimental model. Thus, this study suggested that lignans have a similar mode of action as that of soy-based phytoestrogen, genistein. It has also been reported to play a maximum role in disrupting signal transduction pathways and growth factor transcription by inhibiting tyrosine protein kinase (Yu and Rohan 2000; Chen et al. 2002; Sandhu et al. 2002).

VEGF plays a major role in normal vascular development and tumor progression. Dabrosin et al. (2002) showed that feeding 10% diet of flaxseed to nude mice causes decreased tumor growth by possibly decreasing extracellular VEGF levels. Dabrosin also showed reduced metastatic events with traditional human breast cancer tumors. In this study, researchers contemplated that lignans are the most notable active components in flaxseeds which decrease VEGF through two possible pathways: an estrogen-dependent pathway and estrogen-independent pathway. VEGF consists of estrogen response element (ERE), which contributes to the reduction of circulating estrogens by lignans. Alternatively, lignans in flaxseed may cause decrease in cancer size or restriction of cancer growth through unknown mechanism in which there is an inhibition of hypoxic state. Epidemiologically, *in vitro* and animal studies reported that lignans via various mechanisms like antiproliferative and anti-angiogenic acquire tumor inhibitory properties (Hyder et al. 2000; Dabrosin et al. 2002; Hausott et al. 2003). Several *in vitro* and *in vivo* studies explored the effective role of lignans against colon cancer supporting the antiproliferative activities with decreased tumor number, size, and volume and also suppressed tumor

growth rate. Estrogen-independent growth inhibitory effect was demonstrated in four colon cancer cell lines, namely, LS174T, Caco-2, HCT-15, and T-84, ENL and EDL, each at 100 μM concentrations. A significant association was observed in normalized β-catenin levels with supplementation of 10% rye to Min mice in comparison to wheat-, beef-, or inulin-supplemented diets (Sung et al. 1997; Mutanen et al. 2000; Webb and McCullough 2005).

11.8 Conclusions and Future Prospects

Phytoestrogens are naturally available bioactive compounds widely available in a spectrum of sources such as plant foods. The main dietary sources rich in phytoestrogens are soybean, flaxseed, oil seeds, nuts, kala chana, whole grains, mung bean, red lentils, tofu, green beans, red clover, fruits, and vegetables. They have diverse biological activities because of their capability to behave both as estrogen antagonists and agonists. Phytoestrogens showed both hormonal and non-hormonal activities involved in cancer prevention. The other mechanisms involved in inhibiting the progression of tumor growth are through the embargo of tyrosine protein kinases and inhibition of angiogenesis and DNA topoisomerase 1, which are also involved in the induction of cancer cell apoptosis. In today's world, Westernized diet and lifestyle factors have a major impact in many cancers, particularly colorectal cancer, as it is becoming a worldwide serious health issue. Despite improvements in surgical and chemotherapeutic treatments, colorectal cancer has a poor survival rate. Thus, in this scenario there is a need for natural therapeutic agents with minimal side effects which are required to control the progression of colorectal cancer. Data on the role of PEs in *in vitro* and animal and human studies show that they decrease the risk of different types of tumors. Among them, naturally available bioactive PEs are known to possess antiproliferative and anticancer properties decreasing colorectal cancer and pathologies associated with colon cancer. In spite of a lot of epidemiological and animal data being available that suggest the fact that PEs might show a protective role against colon cancer, the effects observed in colon tumor cell lines should be understood cautiously due to the complications in comparing the exposure of PE to the cells at tissue level in human clinical trials. Data on the suppressing effects of PE on the progress of unchanged normal cells needs to be elucidated if higher concentrations of PE intake are to be extensively recommended. In addition, the exact correlations between dietary PE exposure in humans and the development of cancer need to be explored. Also, there is an urgent need to understand the regulatory mechanisms associated with the absorption of PE and also the interactions with other dietary constituents especially zinc and iron.

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