Chapter 3
Potential of Herbal Medicines in Colorectal Carcinoma and Their Mechanism of Action

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Abstract Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in the world. Although colon cancer is often treated successfully with the surgery, it requires an aggressive systemic therapy to completely cure. Several past studies have suggested the combined use of chemo- or radiotherapy with herbal medicines to enhance the efficacy and diminish the side effects caused by these therapies. In this regard, some herbal compounds such as vinca alkaloids, turmeric, astragalus, ginseng, and ginger have been well studied for their anti-colorectal cancer activities. The identification of active herbal compounds emphasizes on the development of an effective anticancer medicine, which remains as an essential step in the advanced cancer treatments. Many preclinical and clinical studies have proved that herbal medicines are safe, exhibit higher tumour suppressive activity, improve immune system, and increase sensitivity of chemo- and radiotherapeutics. The herbs are more promising as they prevent the invasion and proliferation of tumour by arresting cellular functions. Due to abundance, low cost, and safety in consumption, herbs remain with a tremendous potential to investigate as a combined formulation of chemotherapy to enable tumour growth suppression with less toxic side

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effect and to improve overall survival rate. The aim of the chapter is to focus on various plant and plant-derived compounds showing the promising anticancer activities against colorectal cancer and their potential mechanism of action.

Keywords Adjuvant therapy · Colorectal cancer · Herbal medicine · Mechanism of action

3.1 Introduction

Colorectal cancer (CRC), also known as colon or bowel cancer, develops from any part of the large intestine; begins as clumps of benign cells, called polyps; and may be formed in the last part of the digestive system (colon) or the final segment of the large intestine (rectum). Like other cancer forms, CRC results in an abnormal growth of cells, and it can metastasize (Xie and Itzkowitz 2008; Jemal et al. 2011). The symptoms of CRC vary depending on the tumour location, which may include blood in the stool, change in bowel movements, weight loss, and feeling tired all the time (Cunningham et al. 2010; Jemal et al. 2011). Major factors causing CRC are old age (above 50 years) and lifestyle, and only minor cases are due to genetic disorders. This may result in an altered bowel habits like constipation, diarrhoea, gastrointestinal bleeding, and unsatisfied excretion (Thompson 1989). Rarely, tumour may be very large to fill the entire lumen, like in the case of abdominal distension leading to a visible enlargement of the stomach or as in 'hydronephrosis', that is, distension of renal pelvis calyces resulting in kidney atrophy. CRC is more common in those people who are aged between 60 and 70 years, while cases before 50s are less common except where there is a family history. Persons, who smoke and consume high red meat and less fruits, vegetables, and poultry diets, will develop colon cancer. Alcohol consumption is also a significant risk factor, while regular physical exercise can reduce the chances of colorectal cancer (Chan and Giovannucci 2010). Screening is recommended for men and women over the age of 50; if earlier polyps persist before becoming cancerous, often surgery or chemotherapy is the treatment for CRC (Jasperson et al. 2010).

Growths confined to CRC can be diagnosed through a colonoscopy and/or sigmoidoscopy and, if detected at early stage, is often treatable (Moreno et al. 2016). According to the American Cancer Society report (2017), 90% of CRC cases discovered at this stage will survive a longer period of 5 years. But if tumour spreads into the lymph nodes, the prognosis becomes worse with 48% survival, and if it spreads further, only 7% survival is predictable. CRC is the third most common cancer in men (10% of the total) and the second in women (9.2% of the total) worldwide. It is the second most common cause of cancer death with 42% and 43% impact in both men and women. According to World Health Organization (WHO) report and World Cancer Report of 2014, about 8.2 million patients died from cancer in 2012. It has also been estimated that the number of annual cancer cases would have increased from 14 million to 22 million within the next two decades (Table 3.1).

Table 3.1 Global statistics of colorectal cancer

Incidence and mortality rate worldwide	References
148,810 new cases were diagnosed, accounting for 9% of cancer deaths in women and 8% in men	GLOBOCAN (2012)
1.4 million new cases and 694,000 deaths from the disease	WHO (2017)
26,300 male deaths and 24,530 female deaths	Siegel et al. (2013)
8.2 million patients died from cancer in 2012	WHO (2014)

By 2017, the estimated number of new cases of colon cancer and rectal cancer is 95,520 and 39,910, respectively, adding to a total of 135,430 new cases of CRC with 50,260 estimated deaths (American Cancer Society 2017).

TNM system is a staging tool used to diagnose and determine the stage of cancer for each person as tumour (T), growth of tumour into the wall of the colon or rectum; node (N), spreading of tumour to the lymph nodes; and metastasis (M), cancer metastasized to other parts of the body. Staging is a way of describing where the cancer is located, or whether it has spread and has affected other parts of the body. There are distinct stages described for several types of cancer. There are five stages in CRC, stage 0 (zero) and stages I to IV, which provide a common way of describing the cancer stages as provided by American Joint Committee on Cancer (AJCC) staging shown in tabular form (Table 3.2) (Edge and Compton 2010).

The most commonly used chemotherapy drugs for CRC include antimetabolites (e.g. methotrexate), monoclonal antibodies (e.g. bevacizumab), DNA-interactive agents (e.g. cisplatin, doxorubicin), antitubulin agents (e.g. taxanes), few hormones, and molecular drugs targeting CRC cells (Nussbaumer et al. 2011). However, clinical uses of these drugs are complemented with numerous side effects such as loss of hair, bone marrow suppression, drug resistance, few lesions in gastrointestinal tracts, neurologic dysfunction, and cardiac toxicity. Emphasizing the need for early detection of tumours and development of new and improved treatment regimens, and an increased understanding towards the disease, has reduced the mortality rate nearly by 5% in the last decades (Ramos et al. 2008). The survival of CRC patients depends largely on stage of disease at the time of diagnosis, and it also varies widely between stages (Lozano et al. 2012). The adjuvant (additional) therapy includes the use of herbal plants to reduce considerable risk in patients (Yin et al. 2013). Natural therapies involving medicinal plants and plant-derived products in cancer treatments may reduce the adverse side effects. Currently, many herbal products are being used to treat cancer, and plant products act as a major source of novel chemical structures for the drug discovery. Nowadays, more than 70% of anticancer drugs have their natural origin from plants. At present, a myriad number of plant products have shown their promising anticancer properties *in vitro*, but have yet to be evaluated acutely in humans (Dai and Mumper 2010; Yin et al. 2013; Ahmad et al. 2017). Currently, nanotechnology also aims to enhance the anticancer activities of herbal and herbal-derived drugs to control release of the compound known as nanomedicine, which aim to enhance plant-derived drugs activity (Greenwell and Rahman 2015). Further, studies are required to determine the efficacy of these plant products

Table 3.2 Various stages in CRC, according to American Joint Committee on Cancer (AJCC) (Edge and Compton 2010)

Stages	Stage grouping	Descriptions
0	Tis, N0, M0	The cancer is in its earliest stage. This stage is also known as carcinoma in situ or intramucosal carcinoma (Tis). It has not grown beyond the inner layer (mucosa) of the colon or rectum
I	T1 or T2, N0, M0	The cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0). It has not spread to distant sites (M0)
IIA	T3, N0, M0	The cancer has grown into the outermost layers of the colon or rectum but has not gone through them (T3). It has not reached nearby organs. It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIB	T4a, N0, M0	The cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIC	T4b, N0, M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has not yet spread to nearby lymph nodes (N0) or to distant sites (M0)
IIIA	T1 or T2, N1, M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 1 to 3 nearby lymph nodes (N1a/N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0)
	T1, N2a, M0	The cancer has grown through the mucosa into the submucosa (T1). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
IIIB	T3 or T4a, N1, M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 1 to 3 nearby lymph nodes (N1a or N1b) or into areas of fat near the lymph nodes but not the nodes themselves (N1c). It has not spread to distant sites (M0)
	T2 or T3, N2a, M0	The cancer has grown into the muscularis propria (T2) or into the outermost layers of the colon or rectum (T3). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
	T1 or T2 N2b, M0	The cancer has grown through the mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
IIIC	T4a, N2a, M0	The cancer has grown through the wall of the colon or rectum (including the visceral peritoneum) but has not reached nearby organs (T4a). It has spread to 4 to 6 nearby lymph nodes (N2a). It has not spread to distant sites (M0)
	T3 or T4a, N2b, M0	The cancer has grown into the outermost layers of the colon or rectum (T3) or through the visceral peritoneum (T4a) but has not reached nearby organs. It has spread to 7 or more nearby lymph nodes (N2b). It has not spread to distant sites (M0)
	T4b, N1 or N2, M0	The cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). It has spread to at least one nearby lymph node or into areas of fat near the lymph nodes (N1 or N2). It has not spread to distant sites (M0)

(continued)

Table 3.2 (continued)

Stages	Stage grouping	Descriptions
IVA	Any T, Any N, M1a	The cancer may or may not have grown through the wall of the colon or rectum (any T). It might or might not have spread to nearby lymph nodes (any N). It has spread to 1 distant organ (such as the liver or lung) or distant set of lymph nodes (M1a)
IVB	Any T, Any N, M1b	The cancer might or might not have grown through the wall of the colon or rectum. It might or might not have spread to nearby lymph nodes. It has spread to more than 1 distant organ (such as the liver or lung) or distant set of lymph nodes, or it has spread to distant parts of the peritoneum (the lining of the abdominal cavity) (M1b)

in treating CRC. The aim of the chapter is to focus on the various plant and plant-derived compounds showing the promising anticancer activities and their potential mechanism of action.

3.2 Colorectal Cancer (CRC)

3.2.1 Types and Causes

In CRC, the balance between the rate of cell growth and apoptosis is impaired progressively during disease development. It starts as a benign adenomatous polyp which changes into a propelled adenoma with high-rate dysplasia that advances to aggressive tumour (Simon 2016). Inherited genetic disorders, which can cause CRC, can be distinguished as familial adenomatous polyposis and hereditary non-polyposis colon cancer. However, these might represent only less than 5% of CRC cases. The continuous process of cell division and differentiation of intestinal epithelium can be subverted by genetic alteration that could switch the progenitor cells into tumour cells. Changes in the adenomatous polyposis coli (APC) gene have been linked to about 60% of colorectal neoplasia signifying that APC mutations may be a central event in the development of colorectal carcinogenesis (Abraha and Ketema 2016). Risk factors include older age; male gender; high intake of fat, alcohol, red meat, and processed meats; obesity; smoking; and lack of physical exercise (Johnson et al. 2013). Approximately 10% of cases are linked to insufficient physical activity. The risk for alcohol appears to increase at greater than one drink per day (Fedriko et al. 2011; Mustafa et al. 2016).

Another risk factor is the inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. Drinking five glasses of water a day is linked to decrease the risk of CRC and adenomatous polyps (Lee et al. 2012a). Adenocarcinoma makes up 95% of all CRC cases which includes colorectal adenocarcinoma and gastrointestinal carcinoid tumours. In the gastrointestinal tract, adenocarcinoma develops in the cells of the lining inside the colon and/or the rectum. Among these

rarer types of CRC, gastrointestinal carcinoid tumours grow slowly to form in the neuroendocrine cell and make up to 1% of all CRC, whereas primary colorectal lymphomas develop in the lymphatic system and account for only 0.5% of CRC (Chung and Hunt 2006).

3.2.1.1 Inflammatory Bowel Disease

People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer. The risk increases with how longer a person has the disease and the severity of inflammation. In people with considerable risk, prevention with aspirin and regular colonoscopies are recommended as precaution, while only 2% of people with inflammatory bowel disease turns out to have CRC yearly. In case with Crohn's disease, only 2% get CRC after 10 years, 8% after 20 years, and 18% after 30 years. In ulcerative colitis condition, approximately 16% develops either a cancer precursor or colon cancer in 30 years (M'Koma et al. 2011). Individuals with long-standing ulcerative colitis, an inflammatory disease of the large bowel, are three to four times more likely to develop CRC during their lifetime, compared with those without an inflammatory bowel disease (Rutter 2014; Rutter and Riddell 2014). These individuals also tend to have poorly differentiated carcinomas, which lead to a poor prognosis (Mikami et al. 2011). This link between inflammation and colon cancer is further supported by the association between the use of the anti-inflammatory compound aspirin and reduced colon cancer risk (Chan and Giovannucci 2010; M'Koma et al. 2011). Thus, bowel inflammation and other bowel diseases represent a potentially important target for intervention in colon cancer (Farraye et al. 2010; Rutter 2014; Rutter and Riddell 2014).

3.2.1.2 Genetics

Persons with family history in two or more first-degree relatives (such as a parent or sibling) have a two- to threefold greater risk of disease, and this group accounts for about 20% of all cases. A number of genetic syndromes are also associated with higher rates of CRC; the molecular bases of CRC include familial adenomatous polyposis (FAP), attenuated FAP (AFAP), and hereditary nonpolyposis colorectal cancer (HNPCC). The most common one is HNPCC or Lynch syndrome which is present in about 3% of people with CRC. Other syndromes that are strongly associated with CRC include Gardner syndrome and FAP (Lynch et al. 1993; Jo and Chung 2005). For people with these syndromes, cancer always occurs and makes up 1% of the cancer cases (Jo and Chung 2005). HNPCC consists of at least two syndromes: Lynch syndrome I, with hereditary predisposition for CRC having early (approximately 44 years) onset, with a proclivity (70%) for the proximal colon and an excess of synchronous and metachronous colonic cancers, and Lynch syndrome

II, featuring a similar colonic phenotype accompanied by a substantial risk for carcinoma of the endometrium. There are no known premonitory phenotypic signs or biomarkers of cancer susceptibility in the Lynch syndromes. The most frequent mutations in HNPCC are mutations in the MutS protein homolog 2 (*MSH2*) and MutL homolog 1 (*MLH1*), colon cancer, and nonpolyposis type 2 genes. The former is tumour suppressor gene and more specifically a caretaker gene, with those codes for a DNA mismatch repair (MMR) protein, while the latter one is a component of seven DNA MMR proteins that work coordinately in sequential steps to initiate repair of DNA mismatches in humans. Defects in MLH1 gene are also associated with microsatellite instability (MSI) and an elevated spontaneous mutation rate (mutator phenotype) (Boland and Goel 2010).

Epigenetic factors, such as abnormal DNA methylation of tumour suppressor promoters, play a role in the development of CRC. Although ~75% of colon cancer cases are sporadic, familiar predisposition also plays a vital role in percentage of occurrence of CRC. Germ line mutations in *APC* gene result in the syndrome, FAP, in which affected individuals develop hundreds to thousands of polyps as early as in their teens or early 20s. Individuals with FAP account for only ~1% of all known colon cancer cases, but these individuals have a 100% likelihood of developing cancer unless the colon is removed. The risks of CRC are variable and depend on specific germ line alterations. Fearon and Vogelstein proposed a model, whereby loss of function of *APC* initiates the formation of a benign lesion, followed by an activating mutation in *KRAS* (a proto-oncogene), allelic loss of the 18q locus, and mutation of *p53* gene, which all contribute to the progression to malignant disease. Most deaths due to colon cancer are associated with metastatic disease. A gene that appears to contribute to the potential for metastatic disease is metastasis associated in colon cancer 1 (*MACC1*). It is a transcriptional factor that influences the expression of hepatocyte growth factor. This gene is associated with the proliferation, invasion, and scattering of colon cancer cells in cell culture, tumour growth, and metastasis in mice. Thus, this gene implies to be a potential target for cancer intervention, and these mutations are highly associated with a 100% risk of developing cancer in a lifetime (Zarour et al. 2017).

3.2.2 Signalling Pathways

The risk for CRC is influenced by genetic predisposition, which is especially high for somatic mutations of the tumour suppressor genes, APC, causing familial adenomatosis coli and lifestyle factor. Beyond this, defects in signalling pathways like Wnt signalling pathway and other mutations should occur for the cell to become cancerous. The p53 protein, produced by the *TP53* gene, normally monitors cell division and kills cells if they have Wnt pathway defects. Eventually, a cell line acquires a mutation in the *TP53* gene and transforms the tissue from a benign

epithelial tumour into an invasive epithelial cell cancer. At times, it is not necessary for p53 to be mutated; BAX protein mutation may instead cause the disease (He et al. 2011a). Other proteins responsible for programmed cell deaths that are commonly deactivated in CRCs are transforming growth factor beta (TGF-β) and deleted in colorectal cancer (DCC) in segment of chromosomes. TGF-β has a deactivating mutation in at least half of CRCs. Sometimes TGF-β is not deactivated, but a downstream protein named SMAD is deactivated. To study about various hallmarks hereditary of CRC and its signalling network, naturally mutant or genetically modified animals, such as mutated APC in mice, are primarily used as inducible tumour models. Based on chemical carcinogens, many have been developed to mimic non-hereditary tumour development. Many distinctive models of genetic instability, subsequent clinical manifestations, and pathological behaviour have been characterized to know about different pathways (Esther et al. 2010). Recently, it has been established that many other systems and pathways are involved along with other pathways in the pathogenesis of CRC, which includes abnormal DNA methylation and inflammation, and discovered that microRNA (miRNA) can actively contribute to the carcinogenic process (Colussi et al. 2013; Eliane et al. 2013).

3.2.2.1 KRAS Signalling

The *KRAS* proto-oncogene, a 21-kDa guanosine 5-triphosphate (GTP)-binding protein, initiates the mitogen-activated protein kinase (MAPK) signalling pathway and downstream of epidermal growth factor receptor (EGFR) and another essential component of the EGFR signalling cascade. In 30–40% of CRC, *KRAS* mutations are observed, which shows to be inherently resistant to cetuximab and panitumumab treatment (De Roock et al. 2011). EGFR activates two main intracellular pathways: MAPK pathway and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway. These pathways lead to the activation of various transcription factors that then impact cellular responses such as proliferation, migration, differentiation, and apoptosis (Rosty et al. 2013). High-level expressions of EGFR ligands epiregulin and amphiregulin are also linked to the benefit, resulting from EGFR MAb to therapy in terms of progression-free survival and overall survival in those with KRAS wild-type status (Yarom and Jonker 2011). KRAS is perhaps the only biomarker sufficiently developed for clinical utility; the predictive role of EGFR is limited, particularly for patients being considered for EGFR MAb therapy. To the downstream of KRAS in the MAPK signalling, *BRAF* gene encodes pathway for serine-threonine protein. Mutation in *BRAF* occurs as 5–22% of CRC, when separated by MIS status. *BRAF* mutations are as high as 40–52% of CRCs that arise to MIS pathway to form tumours. In a study with mice, mutations in *TGF-β1* gene were introduced into 129/Sv Rag2 mutant mouse, which accelerates adenocarcinomas with strong local invasion suggesting a role of genetic background in tumour

development. Colon-specific expression of activated mutant of KRAS protein results in development of single or multiple lesions. Oncogenic KRAS allele activated in colon epithelium induces expression of procarcinogenic protein kinase C-βII (PKCβII) and increases cell proliferation of epithelial cells, while in the distal colon the mutant form of KRAS has the opposite effects on PKCβII expression and cell proliferation. When mouse model was treated with the procarcinogen azoxymethane (AOM), it leads to formation of dysplastic microadenomas in the proximal but not in the distal colon, while in the intestine of mice, mutation in the *Muc2* gene causes adenomas and adenocarcinomas.

PIK3CA gene encodes phosphatidylinositol 3-kinase (PI3K), a key signal transducer in the PI3K-Akt pathway. Mutations in *PIK3CA* occur as 14–18% of colon cancers, and most mutations involve hotspots on exons 9 and 20. Interestingly, there is a strong association between *PIK3CA* exon 9 mutations and *KRAS* mutations, and Akt is a major downstream effector of PI3K (De Roock et al. 2011; Rosty et al. 2013). A study by Baba et al. (2011) reported the role of activated (phosphorylated) Akt expression in a large cohort of CRC. KRAS point mutations are generally observed as somatic mutations. Up to 90% of tumour activating mutations of the *RAS* gene are detected in codons 12 and 13, but less frequently also in codons 61 and 63. Regarding codon 12 and 13 mutations, only, 70% of mutations occur in codon 12 and 30% in codon 13 (Al-Shamsi et al. 2015; Módos et al. 2016; Lorentzen et al. 2016). However, KRAS mutation does not appear to account for all drug resistance. NRAS, BRAF, and PI3K activating mutations, as well as loss of PTEN6–9, may also render anti-EGFR-based therapy ineffective, although this is less well established than for KRAS mutations (Lorentzen et al. 2016). The recent success of the selective BRAF inhibitor PLX403222 in metastatic melanoma may herald a new class of targeted agents available for CRC (Grossmann and Samowitz 2011). Previous studies have demonstrated that Ras activation is sufficient to induce vascular endothelial growth factor (VEGF). These data suggest that VEGF may be an *in vivo* survival factor for tumour endothelium (Bruns et al. 2000). In the same study, alterations in PI3K were correlated with poor response, but this association was limited to a small subset of mutations. PI3K mutations have been reported in 15–18% of CRC and all mutations were detected in exon 9 and 20, which blocks binding of p110 catalytic subunit. KRAS testing is essential for determining patient eligibility for EGFR-targeted therapies in metastatic CRC (Li et al. 2016; Lorentzen et al. 2016).

3.2.2.2 Wnt Signalling Pathway

The Wingless-type MMTV integration site family member (Wnt) signalling pathway, the most frequent mutation, is the prominent cause for disease origin in the epithelial cell lining of the colon or rectum of the gastrointestinal tract that increases

signalling activity (Dihlmann and von Knebel 2005; Chiurillo 2015). One of the cadherin protein complex subunit β-catenins acts as an intracellular signal transducer of Wnt signalling pathway, and it is regulated and destroyed by the β-catenin destruction complex, APC protein. Therefore, genetic mutation of the APC gene is strongly linked to cancers and particularly in CRCs resulting from FAP (MacDonald et al. 2009; Fleming et al. 2012). The APC protein, a negative regulator, has been involved in controlling β-catenin concentrations, and it interacts with E-cadherin, involved in cell adhesion (Fleming et al. 2012; Gao et al. 2014; Morkel et al. 2015). Thus, mutations in the APC or β-catenin prevent phosphorylation and β-catenin activation and may result in CRC. Activating mutations of the Wnt signalling pathway are the only known genetic alterations present in early premalignant lesions in the intestine, such as aberrant crypt foci and small adenomas (Morkel et al. 2015; Novellasdemunt et al. 2015).

3.2.2.3 APC Gene

Adenomatous polyposis coli gene, the most common gene mutation in all CRC, produces mutation in APC protein. Around 80% APC mutation is of sporadic colorectal tumours which show diallelic inactivation of the APC gene (Fearnhead et al. 2001). A high percentage of remaining tumours show activating mutations in β-catenin or axin. APC protein prevents the accumulation of β-catenin protein. The normal function of this gene includes the negative regulation of signalling by Wnt cytokines. In the absence of APC function, the Wnt pathway is activated through β-catenin, leading to the transcription of tumour-promoting genes like *Myc* (Walz et al. 2014). Without APC, β-catenin accumulates to elevated levels and translocates (moves) into the nucleus, binds to DNA, and activates the transcription of proto-oncogenes. These genes are normally important for stem cell renewal and differentiation, but when inappropriately expressed at elevated levels, they can cause cancer. Mutation in APC inhibits β-catenin; some cancers show increased β-catenin because of mutations in β-catenin (CTNNB1) which blocks its own breakdown or have mutations in other genes with function like APC such as AXIN1, AXIN2, TCF7L2, or NKD1that results in increased β-catenin in cells (Markowitz and Bertagnolli 2009; MacDonald et al. 2009).

Mouse models of CRC were studied; APC mutant model provided a valuable biological system, to simulate human physiological conditions, suitable for testing therapeutics that can potentially benefit patients. In mutant mouse model of CRC, cyclooxygenase-2 (COX-2) expression was observed in an early event of carcinogenesis. These observations gave rationale to treat human patients suffering from familial form of the disease FAP with selective COX-2 inhibitor (Wang and DuBois 2010). In another experiment, combination of *Min* and *Mom1* mutations was found to increase the lifespan of FAP mouse (Mcilhatton et al. 2016). In zebrafish model, nonsense mutation of APC results in lethality under homozygous condition, while

less than 30% of heterozygous fish developed liver and intestinal tumours during 15 months of age onward. APC heterozygotes of zebrafish were treated with 7,12-dimethylbenz[a]anthracene to enhance tumourigenesis in intestinal, hepatic, and pancreatic tumours, with frequencies three- to fourfold higher than treated wild-types. The tumours displayed activated Wnt signalling, indicating conserved genetic pathway. Other study with two rat models is developed with the polyposis in the rat colon (Pirc) and Kyoto APC Delta (KAD) strains. Each carries APC gene mutations in the intestinal cancer; the heterozygous Pirc strain and the homozygous KAD strain reveal that these models closely mimic APC-dependent neoplasia of humans, and tumours form more frequently in the colon than in the small intestine. This occurs more frequently in males than in females (Irving et al. 2014; Robertis et al. 2011). Thus, it has been implicated in colorectal carcinogenesis, and its stability in the cell is regulated by APC (Schneikert and Behrens 2007; Kwong and Dove 2009).

3.2.2.4 Growth Factors

3.2.2.4.1 EGFR

EGFR has been shown to be overexpressed in colon cancer cell lines and is detectable by immunohistochemistry (IHC) in 70–80% of CRC tumours (Reyes et al. 2014; Mironea et al. 2016). Right-sided colon cancers, which are more often poorly differentiated, express EGFR more intensely than left-sided cancers. Overexpression of EGFR is associated with poor prognosis in most of the studies. EGFR represents an attractive target for anticancer therapies in a variety of malignant neoplasms, including CRC, non-small-cell lung cancer (NSCLC), head and neck carcinomas, and gliomas (Krasinskas 2011).

Recent studies on chemo-refractory colon cancers appear modest increase in copy number (three- to fivefold) present up to 50% of cases; however overexpression of the EGFR and its ligands, TGF-, has been correlated with poor prognosis. Ligand (TGF-) binds to EGFR, causing homo- or hetero- dimerization, enabling downstream signalling. Cancer cells under hypoxia secrete TGF-, thus ligand signals to EGFR in cell surface to stimulate downstream signalling cascade in involving RAS/MAPK and anti-apoptosis (phosphatidylinositol 3-kinase [PI3K]/Akt) and sequentially turn cell survival and cell proliferation. Overexpression of TGF- and EGFR, additionally by carcinomas, is correlated to poor prognosis and cancer metastasis, exhibiting resistance to chemotherapy (Sasaki et al. 2013).

Therapies in CRC treatment involves the EGFR which controls signalling pathways involved in cell differentiation, proliferation, and angiogenesis (Table 3.3). Similarly, overexpression of EGFR alone is correlated with poor differentiation and reduced survival of 1.5 years. EGF, VEGF, and their receptor expression were observed on tumour-associated endothelial cells and have been correlated to

Table 3.3 Components of the EGFR signalling pathway and its importance in CRC

Component (gene/ protein)	Functional protein	Causes/effects in CRC	Frequency of prevalence in CRC patients	Prognostic evidence
EGFR/EGFR	Tyrosine kinase receptor (transmembrane)	Abnormal protein expression, mutation, increased copy number of proteins	More than 90% (25–90%)	Unknown to controversial
KRas/KRas	Ligand-dependent signalling of GDP-/ GTP-binding proteins	Leads to activation of MAPK pathway	30–40%	Controversial
BRAF/B-Raf	Serine-threonine protein kinase (KRAS in downstream)	Mutation in protein	5–12%	MSS tumors-poor prognosis
PIK3CA/ PI3K	PI3K-Akt pathway inhibition	Mutation in exons 9 and 20	14–18%	KRas tumor-poor prognosis
PTEN/PTEN	PI3K inactivation by tyrosine phosphastase enzyme	Loss of heterozygous of protein expression due to mutation	13–19%	KRas tumor-poor prognosis

angiogenesis and tumour progression (López et al. 2012). Hence, inhibition of EGFR signalling pathways represents one of the good strategies for therapeutic intervention for CRC. The antigenic proteins, VEGFA and IL-8, were also strongly expressed in the microenvironment of tumours that produced TGF- (Grossmann and Samowitz 2011; Sasaki et al. 2013). In contrast, expression levels of VEGFA and IL-8 were considered unremarkable in TGF--deficient tumours, while imbalance of macrophages was observed in extracellular matrix (Sasaki et al. 2008, 2013). According to researchers, it is difficult to summarize significance of *EGFR* gene amplification/increased *EGFR* copy number, but studies report that *EGFR* gene is common in CRC. Thus, EGFR has been evolving its role as a prognostic and predictive biomarker in colon cancer (Krasinskas 2011; Joo et al. 2016).

3.2.2.4.2 VEGF

VEGF expression was observed in all surgical specimens, including normal mucosa, primary colon cancers, and metastatic tumours (>20 specimens). Many reports support the hypothesis that VEGF is an important angiogenic factor in all cancer and indicates that the vessel count and the expression of VEGF may be useful in predicting metastasis from CRC (Ellis et al. 2000). Studies with patients determine that it could serve as prognostic markers in node-negative CRC. Those results showed that patient with low VEGF expression had a significantly better survival than patients with high VEGF expression. Thus, VEGF appears to be the predominant angiogenic

factor in human colon cancer and is associated with metastases formation and poor prognosis (Ellis et al. 2000; Bendardaf et al. 2017).

Angiopoietins (Ang) are also expressed by human colon carcinoma. Using reverse transcriptase-polymerase chain reaction (RT-PCR), Ang-1 and Ang-2 expression was measured in normal colonic mucosa, colon cancer specimens, and colon cancer cell lines. Preliminary studies suggest that an imbalance of activity of Ang-2 over Ang-1 may play a role in colon cancer angiogenesis. Results showed a relatively equal frequency of expression of Ang-1 and Ang-2 in all tissues, whereas Ang-1 was not expressed in any of the cancer specimens, while Ang-2 was expressed in all of them. In *in vitro* study, Ang-1 serves as a survival factor for endothelial cells (EC), in conjunction with VEGF to help stabilize vascular networks (Goel et al. 2011; Pafumi et al. 2015). According to Yuan et al. (2009), Biel and Siemann (2016) examined the effect of Ang-1 and observed dose dependently inhibited apoptosis in human umbilical vein ECs (HUVECs), suggesting that Ang-1 acts in conjunction with VEGF and this response was indeed dependent on Tie-2 activation, which might have completely blocked the effects of Ang-1 (Dalton et al. 2016).

SU5416, tyrosine kinase inhibitor of VEGF, led to a decrease in tumour burden and improve survival in mice with liver metastasis. Increases in Src activity are also observed in the majority of colon tumour metastasis (Ellis et al. 2000; Dinarello 2011; Terracina et al. 2015). Studies suggest that the higher expression and specific activity of Src kinase in colon tumour cells can be augmented with the ability of hypoxia to induce VEGF. However, in HT29-AS15 cells, in which c-*Src* expression has been reduced fourfold, the ability of hypoxia to induce VEGF mRNA is severely impaired. These results suggest that in this colon tumour cell system, Src kinase regulates both inducible and constitutive pathways leading to VEGF production. Further confirmation of the ability of Src kinase to regulate inducible VEGF expression was derived from a study of Fleming et al. (1997) in which the ability of cell density was found to up-regulate VEGF expression. Our results suggest that constitutive Src activation may be a primary pathway leading to production of angiogenic factors in colon cancer. Other pathways resulting from genetic changes in colon cancer may also be responsible for the induction of angiogenic factors. These data suggest that the activation of anti-apoptotic pathways mediated by Akt and survivin in ECs may contribute to Ang-1 stabilization of vascular structures during angiogenesis. In another study, Tsai et al. (2015b) and Saif (2013) compared pre- and post-treatment VEGF expression by IHC in 57 patients with mCRC who underwent treatment with 5-fluorouracil (5-FU) and irinotecan (FOLFIRI regimen) combined with bevacizumab. Results indicated that decreased peri-therapeutic, low post-treatment, and VEGF expressions were significant predictors of response to therapy and 6-month progression-free survival (PFS) (Lee et al. 2015).

3.2.2.4.3 IGF

The insulin/insulin-like growth factor (IGF) system is a multifactorial signalling network that modulates energy metabolism, cell growth, and cancer. It consists of a family of six circulating IGF-binding proteins (IGFBPs) that may act as tumour suppressors by limiting IGF activity. According to Firth et al., IGFBPs may have IGF-independent effects on cancer growth, while Edward (2001) suggests multiple markers of hyperinsulinemia (e.g. low physical activity, high body mass index, central adiposity, and high IGF-1 levels) that are also correlated with higher risk of CRC. Followed with these results, the advent of sedentary lifestyle related with obesity and excess carbohydrates and saturated fatty acids increases CRC incidence. Moreover, it has been demonstrated that the increased blood levels of insulin in type 2 diabetes individuals, caused by insulin resistance, enhance the risk to develop colon cancer (Sridhar and Goodwin 2009).

According to Nahor et al. (2005), endogenous IGF-1R levels are reducing in a dose-dependent manner which is directly related to IGF-1R promoter, and hence mutated p63 and p73 are impaired of their ability to suppress IGF-1R in CRC. In case of hyperactivation of the IGF-Rs, HER2, and MET, CRC cells escape EGFR-dependent oncogene mechanism and increase IGF-1R signalling which is with less sensitivity to EGFR inhibition because of functional crosstalk between IGF-1R and the EGFR. Likewise, it is also associated with Akt activation and upregulation of anti-apoptotic protein Bcl-xl and the PI3K/Akt pathway, which was a study based on colon polyps from healthy subjects. In further experimenting with a human CRC cell line over expressing, the IGF-1R-HCT116/IGF-1R resulted in highly invasive tumour and produced distant metastasis in murine models (Vigneri et al. 2015)

People with type 2 diabetes and people with acromegaly, who have elevated levels of insulin and IGF-1, are at elevated risk of colon cancer in most studies (Lugo et al. 2012). Recently, studies that have directly assessed circulating concentrations of C-peptide, 2-h insulin, and IGF found that these predict risk of colon cancer and adenoma. Determinants like physical inactivity, high BMI, central adiposity, and markers like hypertriglyceridemia of insulin resistance and high IGF-1 levels are consistently related to higher risk of colon neoplasia (Vidal et al. 2012). High IGF and low IGFBP-3 are associated with increased risk of several common cancers, including those of the prostate, breast, colorectum, and lung. In addition to stimulating cell cycle progression, IGF-1 also inhibits apoptosis (Livingstone 2013). IGF-1 can stimulate the expression of Bcl proteins and suppress expression of Bax, which results in an increase in the relative amount of the Bcl/Bax heterodimer, thereby blocking initiation of the apoptotic pathway (Shamas-Din et al. 2013).

IGF-1R gene expression partly regulated by p53, but mutation, deletions, epigenetic silencing, or post-translational inactivation unleash IGF-1Rs oncogenic potential. Others like dysregulation of IGF-1 and enhanced activation of IGF-1R are also involved in exhibiting resistance over anticancer therapies like chemotherapy, hormonal agents, biological therapies, and radiation (Wang and Sun 2010). According to Denduluri et al. (2015), multidrug resistance-associated protein 2 (MRP-2) expression increases with IGF-1R signalling; this in turn reduces the intra-

cellular concentrations of multiple cytotoxic drugs. *In vitro* silencing of the IGF-1R suppresses MRP-2 in CRC cells and, thereby, increases the chemotherapeutic effect of intracellular drug concentration of 5-fluorouracil, mitomycin C, oxaliplatin, and vincristine. This effect is also mediated by the PI3K/Akt pathway, which causes nuclear translocation of nuclear factor-like 2 and reduces MRP-2 expression.

3.2.2.4.4 PIGF

Placental growth factor (PlGF) is an angiogenic protein belonging to the VEGF family which is upregulated mainly during the pathologic conditions. Accumulating reports have suggested that PlGF might be a useful prognostic marker of cancer progression. In a study with renal cell carcinoma patients, increased plasma PlGF levels correlate with tumour grade and survival and useful as a prognostic indicator of recurrence and survival in CRC (Van and Pot 2016). mRNA and protein level of PIGF in tumour tissues have also been found to be correlated with tumour stages in lung cancer and progression of disease and survival in case of CRC, with tumour stage and patient survival in gastric cancer, with recurrence, metastasis, and mortality in breast cancer and even with postoperative early recurrence in hepatocellular carcinoma (Kim et al. 2011).

3.2.2.4.5 TGF-Beta

TGF-beta signalling pathway is one of the most prevalent types of mutation during CRC progression. This pathway is involved in numerous processes in the development and homeostasis of adult tissues. This signalling is important in stem cell developments, and nearly all colon cancers have mutations that inactivate pathway components. TGF-beta ligands activate the signalling pathway by binding to TGF-beta receptor type II homodimers. Apoptosis is one of the anticancer effects by arresting cells in G1 stage during cell cycle. Ligand-bound receptor II recruits TGF-beta receptor I homodimers, which are subsequently transphoshorylated and thus activated by receptor type II. Phosphorylation of the intracellular mediator *SMAD* activated receptor I allows dimer formation with SMAD-4 and translocates to the nucleus, where the specific outcome of the signalling will depend on the cell type and the context of the cell itself. Mutations found in CRC affect mainly the TGF-beta receptor type II and the intracellular *SMADS*, SMAD-2, and SMAD-4, by abolishing the transcriptional effects mediated by TGF-beta.

3.2.2.5 Apoptosis

Apoptosis morphologically defined as a form of programmed cell death, a cellular process that is of tremendous current interest to clinicians who study and treat cancer. As a rule, it is thought that the equilibrium between the rates of cell growth and apoptosis sustains intestinal epithelial cell homeostasis, and this stability gets

disturbed during cancer expansion (Wong 2011). Abnormalities in apoptotic function contribute to both the pathogenesis of CRC and its resistance to chemotherapeutic drugs and radiotherapy, both of which act, at least in part, by killing cancer cells (Abraha and Ketema 2016). These epithelial cells have been shown to have a marked tendency to undergo apoptosis following DNA damage. The mechanism by which DNA damage induces apoptosis in the intestine has not been fully elucidated. MDB4 plays a significant role in detecting damage, and coupling this to apoptosis thereby suppresses neoplasia in APC Min/+ mice (Watson 2004; Abraha and Ketema 2016).

The molecular signals that create the stem cell niche at the base of the colonic crypt are currently being identified and have already been implicated in the regulation of apoptosis. Central to this niche is regulation of b-catenin/T-cell factor (Tcf) activity by the Wnt signalling pathway. In the absence of WNT signals, b-catenin is held in a complex with glycogen synthase kinase 3b (GSK3b), axin/conductin, and APC that is rapidly degraded (Stamos and Weis 2013). GSK3b functions to target b-catenin for destruction by ubiquitination. c-Myc, a target of the b-catenin/TCF signalling pathway, has two functional outputs: cell division and apoptosis. The capacity of c-Myc to induce cell division is potent but is not unleashed in normal cells unless apoptotic mechanisms are simultaneously inactivated. c-Myc sensitizes cells to many apoptotic stimuli, including DNA damage, which are sensed through the p53 pathway and mediated by the BH3-only proteins Puma and Noxa together with Bax (Stamos and Weis 2013). During each cell cycle, telomere shortening results in the risk of chromosomal instability (CIN) that increases with chromatin bridge breakage and the fusion of chromosomal ends. This phenomenon of telomere shortening and resultant CIN has been observed in patients with ulcerative colitis who subsequently develop CRC. Of course, normally such a serious genetic error would be expected to trigger apoptosis and thus eliminate the aberrant cell by protective mechanism, including p53 (Wong RS 2011).

The tumour suppressor gene p53 is mutated in 70% of CRCs. It is a transcription factor that binds to specific sequences in DNA and regulates expression of many pro-apoptotic genes (Rivlin et al. 2011). These include Bax and the BH3-only proteins Puma and Noxa. As discussed above, Bax activation inactivates Bcl-2 and Bcl-xL and triggers release of cytochrome c from mitochondria. p53 also increases expression of components of apoptosis effector mechanisms such as APAF-1 and caspase 6. Furthermore, p53 has essential elements of the extrinsic apoptosis pathway as transcriptional targets such as the death receptor Fas and DR5 as well as the BH3-only protein Bid that couples the extrinsic pathway to activation of the intrinsic pathway. It has been estimated that about half of all cancers express the anti-apoptotic proteins Bcl-2 or Bcl-xL. Retinoid, PPARc, and vitamin D receptor agonists all exhibit potential for reducing Bcl-2 or Bcl-XL expression in specific circumstances. Caution must be exercised as PPAR-agonists stimulate colonic neoplasia (Lin and Jian 2013; Alibek et al. 2014).

Ceramide is an important mediator of endothelial apoptosis following high-dose radiation damage, and it is antagonized by basic fibroblast growth factor. The ischaemic damage caused by endothelial apoptosis may be a key mechanism of action of radiotherapy, and apoptosis also plays a vital role as target for cancer treatment

(Lee et al. 2013; Abraha AM and Ketema EB 2016). The increased mitochondrial permeability and release of pro-apoptotic molecules such as cytochrome c into the cytoplasm to induce apoptosis in this pathway regardless of the pro-apoptotic molecules. This pathway is closely regulated by a group of proteins belonging to the Bcl-2 family, the anti-apoptotic proteins (e.g. Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1). Although less thoroughly studied, p53 also trans-represses the important IAP gene survivin which may directly inhibit caspase activity. For example, p53 mutation renders HCT116 colon carcinoma cells more sensitive to Adriamycin and radiation but less sensitive to 5-fluorouracil. A further complication is that p53 appears to respond to RNA damage rather than DNA damage in response to 5-fluorouracil treatment (Pathak et al. 2015).

3.3 Current Treatments for CRC

CRC is the third most common cancer reported with 1200000 newly diagnosed cases each year and the second leading cause of cancer-related deaths with 600,000 deaths annually. Twenty percent of patients diagnosed for CRC with the symptoms unfortunately grow to have metastatic disease (American Cancer Society 2017). Furthermore, ~30% of patients who are diagnosed with early-stage CRC eventually develop metastatic disease. Nowadays overall survival in metastatic patients has improved approximately to 24 months, due to improved efficacy of standard chemotherapy-targeted agents. For more than 50 years, 5-fluorouracil has represented the backbone of all chemotherapy schedules, used both alone and combined (Braun and Seymour 2011; Burotto et al. 2012; Hocking and Price 2014). The addition of oxaliplatin and irinotecan to fluorouracil-based treatment has increased response rate and overall survival (Howells et al. 2010). Nevertheless, chemotherapy alone, reached 18–20 months survival plateau, was obtained by administering alternatively all active cytotoxic agents during treatment strategy (Goldberg et al. 2009; Giordano et al. 2014). Although the median overall survival of patients diagnosed with metastatic CRC has improved from 9 months to 30 months over the past decade, the 5-year OS remains at 5–15%. However, the poor treatment outcome from CRC metastasis patients, sounds for the development of new therapeutic options (Mousa et al. 2015) (Table 3.4).

According to Zeestraten et al. (2013), a five-step program can be used for the development of new biomarkers. Mainly six features are present in cancer cells that distinguish them from normal cells; one of the main characteristics is its ability to escape programmed cell death or apoptosis. Currently researchers are working to identify those key biomarkers in apoptotic pathways to determine cancer prognosis. There are about 26 potential prognostic biomarkers that are directly involved in apoptotic pathway and have been identified till now. In many cases, external death signals triggered by the extrinsic pathway in turn cause the formation of intracellular signalling complexes at the death receptors. This type of apoptosis is typically activated in immune responses. The second pathway, known as the intrinsic path-

Table 3.4 Current major chemotherapeutic drugs used in treatment of CRC

Drug name	Functions	Mechanisms of action	Type of agent	Side effects
Gefitinib	Autophosphorylation	Indirect-EGFR inhibitor	Small molecule inhibitor	Acceptable adverse drug reactions (ADRs)
Erlotinib	Autophosphorylation	Indirect-EGFR inhibitor	Small molecule inhibitor	Acceptable adverse drug reactions (ADRs)
Panitumumab	Tumor-specific antigens; induce apoptosis	Direct extracellular EGFR domain-inhibitor	Monoclonal antibody	Combined with radioactive particle and other anticancer drugs
Cetuximab	Tumor-specific antigens; induce apoptosis	Direct extracellular EGFR domain	Monoclonal antibody	Combined with radioactive particle and other anticancer drugs
Irinotecan	Type I topoisomerase inhibitors	Interferes DNA synthesis	Plant alkaloids (Camptothecin analogs)	Acceptable adverse drug reactions (ADRs)
Oxaliplatin	Cross-link subunits of DNA	Stop DNA synthesis	Alkylating agent (metal salts)	Severe neuropathies
5-Fluorouracil	Interfering with DNA components	Stop DNA synthesis	Antimetabolites (pyrimidine antagonist)	Neurological (CNS) damage
Mitomycin C	Induces ROS and DNA strand break/damage	Cell death	Antitumor antibiotics	Damage lung cells
Vincristine	Inhibits tubulin assembly in microtubules during cell cycle	Cell cycle toxic; inhibits cell division	Plant alkaloids (vinca alkaloids)	Neurotoxicity
Doxorubicin	Induces ROS and DNA strand break/damage	Cell death	Antitumor antibiotics	Cardiac toxicity
Sulindac	COX inhibitor	Indirectly induce apoptosis	Nonsteroidal anti-inflammatory drug (NSAID)	Damage the liver and pancreas; nonfatal myocardial infarction (MI)

way, is activated by many different stimuli, including growth factor deprivation and DNA damage, caused by factors such as UV or gamma irradiation or by chemotherapeutic agents (Ichim and Tait 2016).

3.4 Herbal Medicines in Anticancer Treatment of CRC

The effort for finding new anticancer agents with better efficacy and lesser side effects has gained researcher's interest for decades, and many traditional recommendations and experimental studies have reported anticancerous activities of numerous medicinal plants (Hosseini and Ghorbani 2015). Similarly, numerous studies have also indicated that many herbal medicines can be used along with chemo- or radiotherapy to diminish the side effects and complications in cancer treatment. In this chapter, many herbal medicines that are commonly used for treatment of cancer patients to reduce the toxicity induced by chemo- or radiotherapy (Yin et al. 2013) have been discussed. Alongside, many herbal plants also exhibit anti-proliferative, pro-apoptotic, anti-metastatic, and anti-angiogenic effects of several phytochemicals which have been shown in *in vitro* experiments or animal studies. But only a few medical plants have been tested on patients, and limited evidence exists for their clinical effectiveness (Melo et al. 2011). Mostly localized colon cancer is often successfully treated with surgery; advanced disease requires aggressive systemic therapy that has lower effectiveness. Approximately 30–75% of patients with colon cancer use complementary and alternative medicine (CAM), but there is limited formal evidence of survival efficacy (Hosseini and Ghorbani 2015).

Many herbal medicines possess antioxidant properties. Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species (ROS); they are produced as by-products of biochemical reactions or as signalling molecules which include superoxide and hydrogen peroxides (Lü et al. 2010). When ROS-generating reactions are activated excessively, imbalance between antioxidants and ROS occurs, creating huge quantity of ROS which results in cellular damage. Most of human disease pathogenesis including cancer, aging, and atherosclerosis are directly linked with ROS. It is evident that their damage may be protected by herbal antioxidants which contribute to the total antioxidant defense system of the human body (Li et al. 2015). Previous studies suggest that phytochemicals present in herbal plants may stimulate immunocompetent cells and decrease side effects in patients treated with chemotherapy, but it may or may not affect the levels of antibodies in the blood. One of the essential steps is identifying these herbal sources, to develop better anticancer therapies (Lü et al. 2010; Birben et al. 2012; Nimse and Pal 2015).

Other than phytochemicals, some of minerals and fatty acids present in natural food also have anticancer properties, as chemopreventive agents in colon treatment. Selenium is associated with up to 50% decrease in the risk for colon cancer. It is an important dietary mineral found in broccoli extract, red wine, dietary fibre, pepper, soya, cloves, fenugreek, ginger, apple, and other vegetables. The brassica family of plants synthesizes yellow mustard oil, which also has potential anticancer properties. Mustard contains a complex mixture of long-chain polysaccharides, which may play a protective role in colon cancer formation, and essential oils such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and omega-3 fatty acids are also used to treat and prevent cancer and cardiac diseases. Particularly, the

consumption of fish and fish products reduces the risk of colon cancer progression due to its essential oil content. Vegetables and fruits, rich in fibre content also, may reduce the risk of colon cancer formation (Kuppusamy et al. 2014). Compared to patients treated by chemotherapy alone, patients treated with chemotherapy and herbal extracts showed less likely to experience nausea and vomiting or low white blood cell counts (Kuppusamy et al. 2014). This was proved with an experimental study consisting of 193 patients, up to a 10-year follow-up study by San Francisco Bay-Area centre for Chinese medicine (Pine Street Clinic, San Anselmo, CA). Study done with patients choosing short-term treatment lasts the duration of chemotherapy/radiotherapy than those continuing with long term. Herbal medicine along with vitamins combined with conventional therapy has better effects when compared with conventional therapy alone, which reduced the risk of death in stage I by 95%, stage II by 64%, stage III by 29%, and stage IV by 75%, suggesting that this experiment with prospective trials combining herbal medicine with conventional therapy are justified to be effective (Yin et al. 2013).

3.5 Herbal Plants Against Cancer Mechanism of Action

3.5.1 Crude Plant Extracts and Their Mechanism of Action

3.5.1.1 *Radix astragali*

Radix astragali, frequently used in Asian population as health food supplement, serves as a leading herb in many traditional medicine formulations. The extract of this plant contains total astragalus saponins (AST), the major active constituent found in this herb, and it acts as anticancer agents. AST also shows prominent effects against colon cancer growth. Study, done with HT-29 cell with nude mice tumour xenograft, showed that AST could downregulate circulating VEGF level in serum through inhibition of COX-2, under both normoxic and hypoxic conditions. Study conducted by Law et al. (2012) revealed that AST could significantly reduce tumour growth in nude mice by inhibiting cell proliferation and promoting apoptosis. Similar study with HCT 116 colon cancer cells showed that AST caused PTEN upregulation, reduction in Akt phosphorylation, and subsequent activation of mTOR and suppression of HIF-1α and VEGF under $CoCl_2$-mimicked hypoxia (Lopez-Sanchez et al. 2014). These effects were exaggerated by combined treatment of AST with the mTOR inhibitor rapamycin which could attenuate cobalt chloride-evoked COX-2 activation, while such can cause effect on COX-2 and its downstream target VEGF. In another study, with HCT116 xenografted athymic nude mice, protein level of p-Akt, p-mTOR, VEGF, VEGFR1, and VEGFR2 was downregulated, which effectively reduced COX-2 expression in tumour sections compared to the untreated control (Law et al. 2012; Ran et al. 2016).

Another extract of this plant, Huangqi, is antineoplastic and the most important herb to maintain normal blood levels by the myelosuppressive actions. This is a master herb used in wound healing and may activate telomerase, extending the lengths of the shortest telomeres which protect the terminal DNA at the ends of all chromosomes. This prime herb, which helps in maintaining spleen and lung function, raises WBC count and increases phagocytosis and NK cells; Huangqi is used as intervention with chemotherapy. In a study with decoction of Huangqi, there was a significant reduction of nausea and vomiting in chemotherapy patients and decreased rate of WBC count, increased T lymphocyte (CD3, CD4, and CD8) was observed, but there was no significant difference in immunoglobulins (Taixiang et al. 2005). The decoctions of Huangqi, Chinese herbal medical plant compounds, may stimulate immunocompetent cells and decrease side effects like nausea and vomiting or low white blood cell counts in chemotherapy. This evidence suggests that the decoctions also stimulated cells of the immune system, but did not affect the levels of antibodies in the blood (Cheng et al. 2017). Taken together, these findings suggest that AST exerts anti-carcinogenic activity in colon cancer cells through modulation of mTOR signalling and downregulation of COX-2, which in turn reduce VEGF level in tumour cells that could effectively suppress angiogenesis in both *in vivo* and *in vitro* (Law et al. 2012).

3.5.1.2 Ginseng

Ginseng herb includes genus *Panax* of the family Araliaceae, especially Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), and notoginseng (*Panax notoginseng*) that are used in CRC therapeutics. The major pharmacologically active constituents of ginsengs are ginsenosides, which can be classified as protopanaxadiol and protopanaxatriol groups. In a randomized controlled study, it was found that taking 2000 mg per day of American ginseng (containing 3% of the active ginsenosides) significantly improved fatigue symptoms in cancer patients (Wang and Yuan 2008). Wang et al. (2016) studied the anticancer activities of red Asian ginseng, red American ginseng, and red notoginseng. According to him, the major anticancer mechanisms of red ginseng compounds include cell cycle arrest, induction of apoptosis/paraptosis, and inhibition of angiogenesis. The structure-function relationship analysis has revealed that sugar molecules in ginsenosides inversely impact the anti-proliferative potential of these compounds (Jin et al. 2016). In an assay of American ginseng extract with 5-Fu applied SW-480 cells, extract can heighten the arrest of SW-480 cells in the S phase and increase the cell distribution in G2/M phase compared with 5-FU applied alone. The trend of increasing cyclin A was exhibited, like the increase of S and G2/M phase cells in SW-480 cells. The enhancement of S and G2/M phase arrest, rather than cell apoptosis, might be the mechanism of synergistic effects of ginseng extract with 5-FU (Li et al. 2009a, b). While ERK1/2 reactivation delayed in EGF-stimulated SW-480 cells,

phosphorylated ERK1/2 translocated into the nucleus following its primary activation. It remained in the cytoplasm during late-phase activation leading to protein trafficking, blocked reactivation, and concurrently increased caspase-3 activities and thus improved the efficacy of cancer therapies that target ERK signalling (Joo et al. 2016). Panaxadiol enhanced the anticancer effects of 5-FU on human CRC cells through the regulation of cell cycle transition and the induction of apoptotic cells (Wang et al. 2014, 2015a).

Exposure of HT-29 human colon cancer cells to ginseng extracts resulted in time-dependent inhibition of histone deacetylase (HDAC) activity, results in accumulation of acetylated histones H3 and H4 within cellular chromatin, and enhances more histones to bind to the promoter sequences of the tumour suppressor gene runt-related transcription factor 3 (RUNX3), as well as p21, a downstream target of RUNX3. These alterations were consistent with cell cycle arrest at the G0/G1 phase and induction of apoptosis (Zheng et al. 2013) while they inhibited the phosphorylation levels of the extracellular signal-regulated protein kinases 1/2 (ERK1/2) and (H3) in HCT116 cells (Yang et al. 2016a). These experimental studies provide new insights into the mechanisms of ginseng to human CRC cells. Taken together, these results suggest that the induction of autophagy and apoptosis is mediated through ROS generation and JNK activation in human colon cancer cells (Yu et al. 2015).

The cytotoxic mechanism includes the involvement of ROS and the mitochondrial-involved apoptosis via the modulation of Bax and Bcl-2 expression, resulting in the disruption of the mitochondrial membrane potential. Cytochrome c release from the mitochondria, resulting in the activation of caspase-9 and caspase-3 (Du et al. 2012) and concomitant poly(ADP-ribose) polymerase (PARP) cleavage, which are the indicators of caspase-dependent apoptosis (Lee et al. 2010; Kang et al. 2013, Kim et al. 2013). Decrease in the levels of anti-apoptosis regulator Bcl-2 blocks ROS by inhibiting catalase activation of NF-κB signalling and enhanced ginsenoside like Rh2, Rg3, and Rh2-induced cell death, suggesting that the anticancer effect of Rh2 can be enhanced by antioxidants (Li et al. 2011; He et al. 2011a, b; Kim et al. 2014). American ginseng increased Rg3 and Rh2 content and anti-proliferative activity significantly in NF-kappa B-dependent manner (Luo et al. 2008; Tang et al. 2009; Fishbein et al. 2009).

Mitochondrial damage, increased ROS, and apoptosis in CRC cells via its antioxidants properties with several ginsenosides like Rh2, Rg3, and Rk1 exhibited anti-proliferative and anti-angiogenesis effects *in vivo* and *in vitro*. The mechanisms involved behind this action include NF-kB pathway inhibition of ginsenosides which in turn inhibits cell proliferation and induces apoptosis in cancer cells due to cell cycle arrest in G1 phase and G1/S phase checkpoints (Li et al. 2010; Park et al. 2011). This cell cycle arrest is involved with upregulation of tumour suppressor proteins P53 and P21 tumours and downregulation of cyclin and CDK including the CDK 2, cyclin E, and D1 in G1 phase and G1/S checkpoint (Park et al. 2011; Seo and Kim 2011; Vayghan et al. 2014), thus resulting in apoptosis. Increased apoptosis increases NO production via PI3-kinase/Akt pathway, suggesting an effect of inhibiting angiogenesis (Chen et al. 2014a, ; Han et al. 2016).

3.5.1.3 Mistletoe (Viscum album)

Mistletoe, commonly known as mistletoe, is a semiparasitic woody perennial that grows on several species of tree, including elm, apple, pine, and oak. Mistletoe leaves and young twigs are used by herbalists, and its preparations are made to treat circulatory and respiratory system problems. Animal study and cell line works suggest that mistletoe extract may boost immune system and kill cancer cells. In an experiment, the whole plant mistletoe extract was given to 61-year-old man with a pancreatic adenocarcinoma as once in a week for 5 weeks. After course of treatment, microscopic examination was conducted which revealed dense perivascular lymphocytic infiltrate and increased monocytes, and it protects the DNA in white blood cells (WBC) (Ma et al. 2008).

According to an interesting experiment in University of Adelaide, the researchers conducted an experiment with an extract of mistletoe to focus on whether mistletoe could complement chemotherapy or replace chemotherapy as a treatment for colon cancer. They found that one of the mistletoe extracts, from the *Fraxini* species (which grows on ash trees), was more potent against colon cancer cells in cell cultures compared with other three types of mistletoe extract. It also increased the potency of chemotherapy when used in conjunction. The mistletoe extract was also tested for treatment prolonging survival time of patients with carcinoma of the colon, rectum, or stomach; breast carcinoma with or without axillary or remote metastases; or small cell or non-small-cell bronchogenic carcinoma, and treatment achieved a clinically relevant prolongation of survival time of cancer patients and appears to stimulate self-regulation. Pooled analysis of clinical studies suggests that adjuvant treatment of cancer patients with the mistletoe extract is associated with a better survival. To contradict, another study suggested that mistletoe extract does not seem to be active in metastatic CRC resistant to 5FU/LCV in terms of objective tumour response.

In a retrospective study on 127 patients with CRC, the use of mistletoe extracts was used as possible prognostic indicators. From previous study mistletoe has been established as a potent anticancer agent who could strongly reduce human colon cancer HT 29 cell line growth *in vitro* through MTT bioassay. Hence, randomized controlled study was done on postoperative patients CRC stage; 40 patients in Dukes C and 24 patients in D received 5-FU chemotherapy, six cycles (either the Mayo or the de Gramont protocol). These 64 patients were randomly allocated into three groups as only chemotherapy, for 21 cases; chemo and mistletoe biotherapy for 29 cases and 14 patients underwent only surgery was kept as control group. As a result, they observed that patient treated with chemotherapy and biotherapy had median survival significantly superior to those of patients receiving only postoperative chemotherapy. This finding demonstrates benefit in terms of survival from both combined postoperative chemotherapy and mistletoe biotherapy, either as adjuvant or palliative (Bar-Sela and Haim 2004).

The molecular and cellular mechanism by which mistletoe extracts exerted the cytotoxic and immunomodulatory antitumour effect is largely unknown. Harmsma et al. (2006) studied mistletoe preparations induced tumour regression by cell cycle

inhibition and/or interference with apoptotic signalling pathways in cancer cells. Also, possible effect on angiogenesis, which is a prerequisite for tumour growth *in vivo*, is studied in endothelial cell cultures. Mistletoe caused early cell cycle inhibition followed by apoptosis in a dose-dependent manner. Apoptosis was induced by activating the mitochondrial but not the death receptor-dependent pathway. Mistletoe also seemed to induce apoptosis via the death receptor route, which may explain the higher sensitivity of cancer and endothelial cells to this preparation (Harmsma et al. 2006). Anticancer mechanisms of Korean mistletoe lectin-induced apoptotic human colon cancer cell line reported that cell death was activated due to caspases and inhibition of anti-apoptotic proteins, in part through the tumour necrosis factor receptor 1 signalling pathway. Treatment of human colon cancer cells with mistletoe activated caspase-2, caspase-3, caspase-8, and caspase-9 and decreased expression of anti-apoptotic molecules including receptor interacting protein, nuclear factor-kappaB, X-linked inhibitor of apoptosis protein, and Akt/protein kinase B (Khil et al. 2007; Friedel et al. 2009).

Bock et al. (2014) examined the fatigue levels during first-line chemo- or radiochemotherapy protocols, which were supported by a pharmaceutical mistletoe preparation. Out of 181 patients, 16 patients (8.8%) were diagnosed with CRF in the supportive care group, whereas 86 out of 143 (60.1%) in the chemo- or radiochemotherapy group without supportive mistletoe medication turned with CRF. Clinically, mistletoe medication is the first candidate to be included in a supportive care modus into chemo- or chemo-radiotherapy protocols for colorectal patients to improve CRF without discernible toxicities.

3.5.1.4 Green Tea

Green tea, native to China and India, has been consumed and hailed for its health benefits for centuries globally and one of the most popular affordable drinks in the world. Several health benefits have been explored based on its active metabolites, and antioxidant compounds of green tea play a role in protection against several types of chemically induced cancer in animal models and human on consumption (Babu et al. 2008; Chacko et al. 2010; Hu et al. 2016). Green tea contains a high amount of antioxidant polyphenols, phytochemicals such as heterocyclic amines, flavones, and saponins that can alter xenobiotic-metabolizing enzymes, which effectively controlled cancerous growth in both *in vitro* and *in vivo* models (Kuppusamy et al. 2014; Pampaloni et al. 2014). 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 (Fujiki et al. 2015a; Seif 2016). Regular green tea consumption as three times per week for 6 consecutive months is found to be associated with reduced CRC in non-smokers (Yang et al. 2011). Many biologically active compounds are present in green tea which includes the predominant polyphenols in green tea; (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) have

antioxidant activity. These chemicals, especially EGCG and ECG, scavenge free radicals present substantially and protect cells from DNA damage caused by ROS (Fujiki et al. 2015a, b). Tea polyphenols have shown inhibitory effect to tumour cell proliferation, induce apoptosis in laboratory and animal studies, inhibit angiogenesis and tumour cell invasiveness, protect against damage caused by ultraviolet (UV) B radiation, and improve immune modulatory system function (Babu et al. 2008; Chacko et al. 2010; Yang et al. 2011; Seif 2016).

Reports conducted from many experimental studies support green tea as a chemopreventive agent for CRC, but no quantitative summary of the epidemiologic evidence on the role of green tea and CRC risk has ever been performed. So currently meta-analysis study was performed by Sun et al. (2006) including 25 papers conducted in 11 countries across three continents (North America, Asia, and Europe). From the odds ratios (ORs), highest versus non-tea/lowest tea consumption levels were calculated based on fixed and random effects models, and the meta-regression and stratified methods were used to examine heterogeneity across studies. The combined results from eight studies indicated a reduced risk of CRC with intake (OR = 0.82), effective among three-colon cancer case-control study with OR=0.74, from rectal cancer study OR=0.99, irrespective of study design. Cohort studies of colon cancer (summary OR = 0.99, 95% CI = 0.79–1.24) were compatible with the null hypothesis. Despite the convincing evidence from *in vitro* and non-human *in vivo* studies in support of green tea as potential chemopreventive agents against CRC, available epidemiologic data are compiled in Table 3.5, to conclude various protecting mechanisms of green tea against CRC in humans (Hao et al. 2017).

In conclusion, supplementation of green tea extract (GTE) regulates targeted biomarkers related to CRC specifically to genes associated with WNT signalling (β-catenin), inflammation (NF-κB) and methylation (DNMT1). Combinations with other chemotherapeutic agents provide additional effects compared with either agent alone (Hu et al. 2016). Furthermore, green teas have been shown to activate detoxification enzymes, such as glutathione S-transferase and quinone reductase, which helps to protect against tumour development (Jin et al. 2010). Other beneficial properties including its antioxidant activity also help to prevent cancer, yet its mechanism has not been established. Researchers believe that elevated level of polyphenols in green tea helps to kill cancerous cells and stop them from growing. However, the exact mechanism by which tea interacts with cancerous cells is unknown (Hu et al. 2015a, ; Shin et al. 2017).

3.5.1.5 *Ganoderma Lucidum*

Ganoderma lucidum, medicinal mushroom, is commonly used as Chinese herb and an important ingredient in traditional Chinese medicine herbal formulations. *Ganoderma lucidum* extract (GLE) is rich in antioxidant activity, while anti-proliferative effect of extracts was observed in SW480 cells, and it also possess anticancer effect and may also help to decrease chemotherapy-induced side effects. GLE-1 inhibited DNA synthesis in the cells and reduced the formation of free radicals

Table 3.5 Role of green tea extracts as anticancer agent

Green tea constituents	Model	Activity	Causes/signalling pathway involved	Gene involved	References
EGCG, polyphenolic constituent	HT-29	Inhibits growth, invasion, and metastasis (tumorigenesis)	–	Matrix metalloproteinase (MMP7, MMP2, MMP9)	Kim et al. (2005)
		Inhibits topoisomerase I	Induces DNA damage, cell cycle arrest, and causes apoptosis	Anti-proliferative agent	Berger et al. (2001) and Hajiaghaalipour et al. (2015)
		Inhibits receptor tyrosine kinases	Inhibits tyrosine receptors IGF/IGF-1R and VEGFR2	IGF, IGF-1R, VEGF, VEGR, EGFR, HER2, and HER3	Shimizu et al. (2011)
	SW837 cells	Inhibition of tyrosine kinases receptor	Decreased IGF-1R and IGF-1 protein and increased IGFBP3 protein	Increase in the expression of TGF-beta2	Shimizu et al. (2005a, b)
		Non-steroidal anti-inflammatory drugs (NSAIDs)	Regulatory role of AMP-activated kinase (AMPK) in COX-2 expression	Decreased COX-2 promoter activity via inhibition of nuclear factor kappaB (NF-kappaB) activation	Peng et al. (2006), Hwang et al. (2007), and Park et al. (2009)
		Reactive oxygen species (ROS)			
	Mice (nude mice) cells	Inhibits cell proliferation	APC/b-catenin	Decreased COX-2, c-MYC, and cyclin D1 protein	Patel et al. (2008) and Sukhthankar et al. (2008)
				Reduced bFGF expression	
		Inhibits APC	Adenomatous polyposis coli (APC)	Repressed expression of cyclin D1, c-myc, and degradation of β-catenin	Oh et al. (2014), Chen et al. (2017), and Kim et al. (2017b)
			Downregulates Wnt/β-catenin		
		Inhibition	Mitogen-activated protein kinase (MAPK) and Akt pathways	Kinase inhibitors, Akt, ERK1/2, or alternative p38MAPK activity	Cerezo-Guisado et al. (2015)
		miRNA		Suppressed notch1, Bmi1, Suz12, and Ezh2 and upregulated self-renewal suppressive-miRNAs, miR-34a, miR-145, and miR-200c	Toden et al. (2016)

	HCT-116 cells	Hypoxia condition	Inhibits HIF-1 alpha	Suppressed NF-kB, VEGF/VEGFR expression	Navarro-Perán et al. (2008), Shimizu et al. (2010), and Sukhthankar et al. (2010)
		Methylation-sensitive colon cancer cells	Apoptosis	E3 ubiquitin ligase, UHRF1	Moseley et al. (2013)
Green tea extract + protopanaxadiol (PPD)	HT29 cells	Enhances antioxidants of GT	Inhibits the activation of NF-κB signalling	Tumor controls	Wang et al. (2013)
EGCG and Poly E	HT29 cells and FHC cell line	Inhibits phosphorylation of protein	Kinase and Akt signalling	Decrease EGFR and HER2, NFk-B, Cyclin D1, HER2, and HER3	Shimizu et al. (2005a) and Xu et al. (2010)

(Xie et al. 2006). To confirm cancer-preventive effects of GLE, Oka et al. (2010) performed a no-treatment and GLE-treated controlled trial on patients with colorectal adenomas, which inhibited G2/M phase of cell proliferation through downregulation of cyclin A and B1 and upregulation of p21 and p27, revealing tumour shrinkage of CRC in nude mice (Hsu et al. 2008; Na et al. 2017)

The mechanistic effects of GLE were focused on the PI3K/Akt/mammalian target in IBC SUM-149 cells, which resulted in reduced expression of mTOR, and its downstream effectors at preliminary treatment time, with time eIF4G levels, are reduced which was coupled with increased levels of eIF1E and reduced protein synthesis (Suarez-Arroyo et al. 2013). Moreover, there was greater degree of reduced small intestinal damage in 5-FU plus GLE-treated rats than in 5-FU alone treated, and regulation of cell survival and growth was observed in IBC SUM-149 cells. This results in reduced expression of mTOR indicating that GLE could have potential to be used as agent against colonic precancerous lesions and to treat the common adverse effects of chemotherapy (Watanabe et al. 2013). Potent anti-proliferative and anti-colony formation activities were exhibited on HT29 and HCT116 CRC, by inducing cell cycle arrest in G1 phase through the regulation of cyclin D1 and P53 expression, while in HCT-116 cells by inducing cell apoptosis and activating unfolded protein response and caspase-9 regulated pathways. During stress condition, cancer cells undergo autophagy, a stress adaptation mechanism which is suppressed by GLE treatment; hence apoptosis of HT29 cells might be triggered by GLE (Thyagarajan et al. 2010; Dan et al. 2016). In another study, GLE reactivated mutant p53 in CRC HT29 and SW480 cells while applied alone or together with 5-fluorouracil (5-FU). This reactivation further induced cell growth inhibition and apoptosis (Jiang et al. 2017; Na et al. 2017).

HCT-119 cells were used to study GLE antitumour activity; according to Liang et al. (2014), increased level of caspase-8 activity was observed which is related to apoptosis. Fas and caspase-3 protein expression was upregulated after GLE treatment. This was the first experiment demonstrating GLE mechanism through elevated intracellular calcium release and the death receptor pathway (Liang et al. 2014). According to study conducted by Kim et al. (2015b), Khz (a fusion mycelium of G. lucidum and Polyporus umbellatus mycelia), cytotoxicity was measured using MTT assay and found that Khz suppressed cell division and induced apoptosis via mitochondrial disruption by changing membrane potential, increasing calcium concentration and ROS generation. Increased caspase-3, PARP, caspase-7, and caspase-9 levels, but reduced Bcl-2 protein levels, lead to reduced cell viability. The activation of caspases-3, caspase-8, and caspase-9 is involved with GLE-stimulated apoptosis. Additionally, treatment with GLE promotes the expression of Fas and caspase-3 proteins while reducing the expression of cleaved poly(ADP-ribose) polymerase. As a result antitumour activity of CRC cells was observed through inhibition of migration and induction of apoptosis (Qi et al. 2010; Liang et al. 2015).

3.5.1.6 *Phyllanthus Watsonii*

Phyllanthus watsonii Airy Shaw is an endemic plant found in Peninsular Malaysia, although anticancerous property has been reported earlier, but cytotoxicity effect was report very less. The lignan compound, phyllanthin, is the known principal constituent, while sterol glucoside was also being detected from various marine organisms and alga was reported to possess few cytotoxic activities. Extracts show strong cytotoxicity and high sensitivity towards human gynaecologic and colon cancer cells when compared to normal lung fibroblast cells. Cytotoxic and apoptotic potential of the endemic *P. watsonii* was investigated for the first time by bioassay-guided approach, which indicated that extracts have arrested cell cycle at different growth phases in SKOV-3, Ca Ski, and HT-29 cells (Ramasamy et al. 2012). Extracts on human breast cancer cell MCF-7-induced cell death were mainly due to apoptosis, which is characterized by morphological changes, nuclear DNA fragmentation, and caspase-3 activation. Following *P. watsonii* extract treatment, evident of apoptotic cell death was observed which was preceded by S phase cell cycle perturbation.

3.5.2 Isolated Plant Extracts: Phytoproducts and Its Action Mechanism

3.5.2.1 Curcumin

Curcumin is a naturally occurring powerful anti-inflammatory medicine and active ingredient present in the spice turmeric. It has been shown with anticancer properties in various animals and cell culture studies (Patel et al. 2010). Epidemiological data shows incidence of CRC is lower in countries with regular use of turmeric, which is present in spicy curry dishes. Bowel disorders in combination with phytochemicals was found to inhibit colon cancer cells from multiplying and spreading by inhibiting the cytochrome P-450 enzyme activity (Hamam 2014). The antitumour effect of curcumin has been attributed in part to the arrest of cancer cells in S, G2/M cell cycle phase, inhibits the growth of DNA mismatch repair, and induces apoptosis in CRC (Sa and Das 2008). Curcumin shows inhibitory effects upon Cox-2 and cyclin D1 which is mediated through NF-κB restricted tumour cell growth. It can also downregulate the expression of various other pro-inflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, through inactivation of the transcription factor NF-κB (Mao et al. 2007). With its ability to inhibit the growth of neoplastic cells via various mechanisms, curcumin is king against colon cancer.

Curcumin is the most important secondary metabolites for its anti-carcinogenic properties. It affects protein expression in molecular level and controls cancers cells via COX-2, VEGF, IL-1, IL-6, IGF, and chemokines. It shows lipoxygenase activity against cyclooxygenase-2 (COX-2) expression in malignant cells, and it modulates the action of TNF-α and NF-κB factors. Preliminary observations on COX-2 expression in inflammatory bowel disease (IBD) is correlated to colorectal neoplasia; gen-

esis and progression were clinically reduced with antitumour effects of curcumin. It has the ability to reduce pro-caspase-3 levels, polymerase-1 cleavage, and chromatin condensation. In a time- and dosage-dependent manner study, curcumin caused wild-type p53 HCT-116 cells to self-destruct, while HT-29 cells show a manner inhibition of COX-2, but not COX-1 (Howells et al. 2010). Curcumin selectively destroys cancer cells by triggering the death pathway by increasing the level of protein called genes activated during DNA damage (GADD45a). Despite p53 upregulation and activation, curcumin-induced apoptosis in colon cancer cells occurs independent of p53 status and oxidative stress, independently via G2/M phase arrest (Watson et al. 2010; He et al. 2011b).

According to Rahmani et al. (2014) and Shanmugam et al. (2015), curcumin reduced the indirect association of cortactin, and it significantly decreases the pTyr421-CTTN in HCT116 cells and SW480 cells, but was ineffective in HT-29 cells. It physically interacted with PTPN1 and activates it to reduce cell motility in colon cancer via dephosphorylation of pTyr421-CTTN (Radhakrishnan et al. 2014). It also promotes caspase-3-mediated cleavage of β-catenin, decreases β-catenin/Tcf-Lef transactivation capacity for c-Myc and cyclin D1, and activates caspase-7 and caspase-9 which induce downregulation of NF-κB. Furthermore, it inhibits EGFR activation, Src activity, and activity of some nuclear receptors (Vallianou et al. 2015). It also acts as a potent immunomodulatory agent by activating both immune system via T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. The molecular mechanism of action of curcumin is via (1) Wnt/β-catenin, sonic hedgehog, notch, and PI3K/Akt/mTOR signalling pathways, (2) microRNA, and (3) multiple level at epithelial-mesenchymal transition.

Thus, curcumin acts as chemosensitizer towards CRC stem cells, and hence they sensitized anticancer therapy. Combination therapy using other anticancer agents like chemotherapeutic agents or other herbal agents, along with curcumin, might be more effective, for example, agents such as silymarin along with curcumin treatment result in high amount of cell death, compared with single treatment (Thamil et al. 2015). In a clinical study conducted, patients showed clinical benefits after administration of curcumin doses of up to 2.2 g per day for up to 4 months reduced bowel polyps. The anticancer effects of curcumin and its derivatives have typically been attributed to inhibition of cell proliferation, cell cycle arrest, and/or induction of apoptosis. It expresses antitumour activity by altering the deregulated cell cycle via (a) cyclin-dependent, (b) p53-dependent, and (c) p53-independent pathways. This provides explanations for how curcumin reverses the multidrug resistance (MDR) of cancer cells (Tuorkey 2014). Curcumin is a potent cancer fighter; through several mechanisms, it can kill a wide range of tumour cell types including MDR cancer cells.

3.5.2.2 Resveratrol

Resveratrol (trans-3,5,4-trihydroxystilbene) is a phytoalexin, toxic compound that is synthesized by plants in response to stress and invasion of other pathogens (Patel et al. 2010). This compound has anti-inflammatory, anti-oxidant, and anticancer activities. This plant-derived ellagic acid has previously been identified as a potent

anticancer agent with molecular targets as NF-kB, cyclin D1APC, and TP53 found in CRC (Doonan et al. 2017), and COX-2 protein observed to be inhibited when cells are treated with resveratrol (RSVL) (Chen et al. 2012; Gong et al. 2017). The grape bioactive compound RSVL potentiates grape seed extract (GSE)-induced colon cancer cell apoptosis at physiologically relevant concentrations like sulindac, without any gastrointestinal toxicity. This RSVL-GSE treatment also reduced the number of crypts containing cells with nuclear β-catenin (an indicator of colon CSCs) via induction of apoptosis by elevated p53, Bax/Bcl-2 ratio, and cleaved PARP (Reddivari et al. 2016).

Experiments were carried on HCT-116 cells to evaluate anticancer potential of RSVL and its action mechanism involved. According to Karimi Dermani et al. (2017), RSVL controls tumour growth through upregulation of miR-200c by regulating apoptosis, invasion, and switching of EMT to MET phenotype in CRC. In other study, p53 and BAX gene expression were elevated after RSVL treatment, suggesting arrest of cell cycle during G2/M phase (Demoulin et al. 2015; Khaleel et al. 2016). Cancerous cells exhibit increased Shh signalling causing increased HCT116 cell viability and migration, inhibited cell apoptosis, and upregulated the expression of Ptch, Smo, and Gli-1. When these were exposed to RSVL, it promoted cell apoptosis and suppressed the protein Ptch, Smo, and Gli-1, which may be mediated by hedgehog/Gli-1 signalling pathways (Du et al. 2016). A synthetic analogue of resveratrol, labelled as HS-1793, can inhibit cell growth and induce apoptotic cell death in a concentration-dependent fashion via cleavage of poly(ADP-ribose) polymerase, alteration of Bax/Bcl-2 expression ratio, and caspase activation (Kim et al. 2017b). In HT-29 cells, the expression of Bcl-XL gene was significantly increased after exposure to RSVL, causing controlled growth possibly by arresting cell cycle in S phase (Schroeter et al. 2015; Khaleel et al. 2016). RSVL shows arrest of cell cycle in the G0/G1 phase and promotes cell apoptosis in colon cancer stem cell-related studies done by Yang et al. (2015). In *in vitro* study, TGF-β1-induced EMT promoted the invasion and metastasis of CRC, reduced the E-cadherin expression and elevated the vimentin expression, and activated the TGF-β1/SMAD signalling pathway (Ji et al. 2015).

CRC when exposed to RSVL significantly inhibits cyclooxygenase-2, indomethacin, and prostaglandin receptor expression (Feng et al. 2016), topoisomerase (TOP) II (Schroeter et al. 2015), inhibition of epithelial-mesenchymal transition (EMT) factors (increased E-cadherin), transcriptional activity of cAMP-responsive element (CRE) (Wang et al. 2015c; Scherzberg et al. 2015), downregulation of NF-κB activation (MMP-9, caspase-3) (Buhrmann et al. 2015), and WNT signalling (Holcombe et al. 2015). These findings enhance the usage of RSVL to develop strategies for diet-derived agents designed to achieve cancer chemoprevention (Del et al. 2013; Cai et al. 2015). Mechanistic study demonstrates RAH inhibits cell cycle arrest through downregulation of cyclins and induces apoptosis by activation of caspase-3 in cancer cells, highlighting the improved anticancer properties of resveratrol-based aspirin prodrugs (Bottone and Alston-Mills 2011; Zhu et al. 2015). The molecular mechanisms are studied for the CRC chemopreventive activity of NSAIDs (i.e. aspirin, sulindac, and ibuprofen), COX-2 inhibitors (i.e. celecoxib), natural products (i.e. curcumin, resveratrol, EGCG, genistein, and baicalein), and metfor-

min. Thus, this provides a new mechanistic link between resveratrol and tumour downregulation and its significant benefits. A deeper knowledge of this anti-inflammatory agent's mechanism will provide insight into potentially safer drug (Fajardo and Piazza 2015; Jeong et al. 2015). One of the new findings provided evidence that resveratrol could inhibit EMT in CRC through TGF-β1/SMAD signalling pathway mediated Snail/E-cadherin expression (Ji et al. 2015; Osman et al. 2015).

Sporadic and nonhereditary mutations are the major causes in CRC; the loss of APC function and activation of the β-catenin/LEF signalling pathway, activating mutations in KRAS, are major causes in sporadic CRC. Thus, resveratrol can prevent the formation and growth of CRC by downregulating KRAS expression in sporadic case (Saud et al. 2014). The exogenous expression of PTEN inhibits the PI3K/Akt signal and promotes the anti-proliferative effects in HCT116 cells, whereas knockdown of PTEN increases PI3K/Akt signalling but reduces the anti-proliferative function of RSVL that may be mediated by regulating separately the PTEN/PI3K/Akt and Wnt/β-catenin signalling (Vanamala et al. 2010; Liu et al. 2014; Aires et al. 2013). RSVL also cause reduction of immune cells and cancer cells jointly in a dose-dependent production of cytokines (IL-6, IL-1ra, and IL-10) (Bergman et al. 2013). Overall, the clinical evidence of dietary phenolics against CRC is still weak, and the amounts needed to exert some effects largely exceed common dietary doses (Tak et al. 2012; Núñez-Sánchez et al. 2015).

3.5.2.3 Betulin

Recent clinical studies have shown that betulinic acid (BA) was effective against a variety of tumours by either inducing apoptosis and/or slowing the cell division (Alakurtti et al. 2006). BA has significant inhibitory effect on VEGF expression in human CRC xenografts in *in vivo* model (Ren et al. 2010). The mechanism of action of BA was dependent on cell context as proteasome-dependent and proteasome-independent downregulation of Sp1, Sp3, and Sp4 in SW480 and RKO cells, respectively. In RKO cells, the mechanism of BA-induced repression of Sp1, Sp3, and Sp4 was due to ROS-mediated repression of microRNA-27a, and induction of the Sp repressor gene ZBTB10, suggesting the anticancer activity of BA against CRC (Chintharlapalli et al. 2011; Su et al. 2017).

BA could induce autophagy and proteasomal degradation pathway in HT-29 cells (Dutta et al. 2016). It is a novel class of selective PPAR gamma modulators with potential for clinical treatment of colon and pancreatic cancer (Chintharlapalli et al. 2007). It has been found to activate two human apoptotic pathways: the mitochondrial apoptotic pathway and NF-κB pathway. DNA damage activates NF-κB. NF-κB leads to inflammation and the synthesis of ROS, cytokines, and chemokines including TNF, lymphotoxins, IL-6 and IL-8, and growth and angiogenic factors. NF-κB can lead to malignant proliferation, prevention of apoptosis, and an increase in metastasis and angiogenesis (Mullauer et al. 2011). In study based on *in vitro* sensitivity of cell line on BA, prevalent cancer-type cell line panels derived from lung, colorectal, breast, prostate, and cervical cancer were performed

to show a highest mortality in women and men cell types. These results substantiate the possible application of BA as a chemotherapeutic and/or adjuvant agent for the most prevalent human cancer types (Kessler et al. 2007; Potze et al. 2016).

3.5.2.4 Silibinin

Silibinin, a polyphenolic flavonoid, is the major biologically active compound of milk thistle. Silibinin (SB) and its crude form, Silymarin (SM), are used clinically and as dietary supplements against liver toxicity. Studies have demonstrated the inhibitory effects of silibinin on multiple cancer cell lines including human CRC. The anti-angiogenic effects of SM/SB are associated with the upregulation of VEGFR-1 (Flt-1) gene expression, another viable candidate for combination therapy to treat CRC (Yang et al. 2005). The protein bid was cleaved in SW480 cells indicating crosstalk between extrinsic and intrinsic apoptotic pathway, overwhelmed by the activation of both the extrinsic and intrinsic apoptotic pathways (Kauntz et al. 2011).

First, SB rapidly induced oxidative stress in CRC, SW480 cells due to ROS generation with a concomitant dissipation of mitochondrial potential and cytochrome C release leading to mild apoptosis as a biological effect, suggesting that SB harbours a deadly 'double-edged sword' against CRC cells, thereby further advocating its clinical effectiveness against this malignancy (Raina et al. 2013a, b; Kumar et al. 2014). Taken together, these data indicated that silibinin inhibits LoVo cell invasion with the reduction of MMP-2 presentation by attenuating AP-1 binding activity, as novel anti-metastatic compound against CRC (Kaur et al. 2009; Lin et al. 2012; Wang et al. 2012). Oral feeding of silibinin on NF-κB pathway in SW480 (COX-2 negative) and LoVo (COX-2 positive) tumour xenografts in nude mice showed inhibitory efficacy on tumour growth and progression via NF-κB activation in both xenografts (Sangeetha and Nalini 2015). Together, these findings are highly significant in establishing for the first time that SB suppresses CRC growth and progression possibly through its anti-inflammatory activity by interfering with NF-κB activation and thus has potential against human CRC (Raina et al. 2013a).

In a comparative study between the effect of chrysin and SB on HT-29 cells, chrysin caused cell cycle arrest in G2/M phase, while SB activated caspase-3 triggers the cells directly to apoptosis. Moreover, SB diminished the NF-kB activation by increasing the sensitivity of cells to apoptosis, and it inhibited topoisomerase IB activity concluding that this is an important target involved in the anticancer vanadium effects. Thus, the result represented that silibinin has a stronger and deleterious action than chrysin on HT-29 cells (León et al. 2015). The combined treatment of Colo 205 cells with metformin and SB induced apoptosis in human CRC cells at a dose that does not affect human colonic epithelial cells (HCoEpiC). This finding reveals a potential therapeutic strategy of SB for the treatment of CRC (Tsai et al. 2015a). Silibinin also restores promoter activity from a vitamin D response element (VDRE); 1,25D had no significant effect on HT-29 and SW480-R cell proliferation and migration, while co-treatment with SB restored 1,25D responsiveness to decreased proliferation and migration (Raina and Agarwal 2013). These findings

demonstrate that this combination may present a novel approach to target CRC in conditions of chronic colonic inflammation (Bhatia and Falzon 2015). Thus, over the years, preclinical studies have shown that SB has strong preventive and therapeutic efficacy against various epithelial cancers, including CRC (Raina et al. 2016).

3.5.2.5 Tanshinone

Tanshinone (Tan) is one of the most abundant diterpenes isolated from *Salvia miltiorrhiza Bunge* (Danshen in Chinese). It has been shown to possess many pharmacological activities like antioxidant, protecting and/or preventing angina pectoris and myocardial infarction (Lee et al. 2012b). Report has also shown its proliferative inhibition and cytotoxic effects on cell lines derived from various human carcinomas and also a significant percentage of reduction in the mortality of patients suffering from alcoholic liver cirrhosis.

Tanshinone IIA (Tan IIA) lowers HIF-1α levels and inhibits secretion of VEGF and bFGF, but also efficiently suppresses the proliferation, tube formation, and metastasis in colon cancer (Shan et al. 2009). Interruption of the HIF-1α/β-catenin/TCF3/LEF1 signalling pathway which occurs in the hypoxic microenvironment is disturbed by Tan IIA. Finally, Tan IIA sodium sulfonate exhibits anti-angiogenesis activity in CRC patients by reducing levels of angiogenin, VEGF, and bFGF expression (Sui et al. 2017). Tanshinone IIA also significantly inhibited *in vivo* metastasis of colon carcinoma SW480 cells by reducing levels of urokinase plasminogen activator (uPA) and matrix metalloproteinases (MMP)-2 and MMP-9 and by increasing levels of tissue inhibitor matrix metalloproteinase protein (TIMP)-1 and TIMP-2 and inhibition of the NF-kappaB signal transduction pathway, and also it inhibits the proliferation in Colo 205 cells, through downregulation of ErbB-2 protein and upregulation of TNF-alpha and caspase-3 (Su et al. 2008a; Su and Lin 2008; Zhang et al. 2016). In a study, COX-2 promoter and COX-2 plasmids were transfected into HCT-116 cells, and the result showed that Tan IIA could inhibit tumour growth and suppress VEGF level *in vivo* and exerts inhibitory effect on COX-2 and VEGF in a dose-dependent manner (Zhou et al. 2012).

The expression of p53, p21, bax, and caspase-3 increased in tanshinone IA (Tan IA)-treated cells, and the cell cycle analysis showed G0/G1 arrest in Colo 205 cells, suggesting Tan IA work through both mitochondrial-mediated intrinsic cell death pathways and p21-mediated G0/G1cell cycle arrest (Su et al. 2008b). Tan IA was also known to induce apoptosis in CRC cell lines, but interestingly, Tan I did not exercise much inhibitory effect on normal colon epithelial cells or CRC cells with mutant p53, indicating relative selectivity towards CRC cells with full normal p53 (Lu et al. 2016). Tan IA induce apoptosis through inducing caspase-3/caspase-9; a crosstalk between cytochrome c and apoptosis-inducing factor (AIF) was also reported (Wang et al. 2015b). Multidrug-resistant colon cancer cells SW620 showed increased viability after autophagy inhibition, indicating that autophagy induced by the two tanshinones was pro-cell death (Hong et al. 2017). These two tanshinones induce cell death in a p53-independent pathway, which could be useful in inhibiting the growth of apoptosis-resistant cancer cells with p53 defects (Hu et al. 2015b).

Results from Liu et al. (2013) and Kim et al. (2015a) studies suggest that Tan I-mediated cyclin D1 downregulation may result from proteasomal degradation and through its ERK1/2-mediated phosphorylation of threonine-286 which provides new mechanistic link between Tan I, cyclin D1 downregulation, and cell growth in human CRC.

Tanshinone IIA also inhibits the production of inflammatory cytokines, tumour necrosis factor α (TNF-α), and interleukin 6 (IL-6), which generated by macrophage RAW264.7. microRNA-155 (miR-155) was upregulated in macrophages, and it could be a potential target for the prevention of inflammation-related cancer (Tu et al. 2012; Gavrilas et al. 2016). Tan-IIA plus 5-FU could be used as potential therapeutic agents for human CRC, as it causes a reduction in the xenograft tumour volumes and decreased P-glycoprotein (P-gp) and microtubule-associated protein light chain 3 (LC3)-II expression compared to 5-FU alone (Su 2012; Chen et al. 2014b). These result promising Tan IA and IIA as a leading compound for the development of antitumour agent or are developed as an adjuvant drug for colon cancer therapy (Liu et al. 2013).

3.5.2.6 Quercetin

Quercetin is a natural antioxidant derived from fruits and plant resources and is a bioactive compound with anti-inflammatory, antioxidant, and anticancer properties. This flavonoid is rich in onions, tea, and apples, and they effectively induce apoptosis and suppress the proliferation of cancer cells in both *in vitro* and *in vivo* CRC studies. The proliferation, apoptosis, and differentiation processes are shown to be dysregulated in HT-29 and HCT15 cells when investigated with quercetin during cancer (Del et al. 2013). Activation of caspase-3 leads to increased cytosolic cytochrome c, which in turn decreased pAkt, pGSK-3β level, and cyclin D1 development. Though nuclear translocation of NF-kB and overexpression of ROS and COX-2 were observed in HT-29 cells, quercetin-treated HCT15 cells did not expressed COX-2. In-silico analysis provides evidence that partial inhibition of COX-2 enzyme is due to quercetin binding to COX-2 subunit A, which has peroxidase activity and serves as source of ROS (Raja et al. 2017; Zizkova et al. 2017).

MTT assay was conducted to investigate the effects of quercetin on HT-29 CRC cells, which showed cell shrinkage, chromatin condensation, and nuclear collapse in a dose-dependent manner. Significant cell cycle arrest in the S phase and increased CSN6 protein degradation were also observed. Therefore, this affects the expression levels of Myc, p53, B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein suggesting quercetin-induced apoptosis (Atashpour et al. 2015; Yang et al. 2016b). The TEF (5,3′-dihydroxy-3,7,4′-triethoxyflavone), a newly synthesized quercetin derivative, has also been evaluated on HCT-116 cells to induce apoptosis. It is confirmed by the presence of fragmented nuclei, reduced mitochondrial membrane potential, and elevated cytoplasmic and mitochondrial ROS levels. Molecularly TEF treatment causes elevation of IRE1-α and activates calcium ions (Ca^{2+}) with concomitantly increased JNK levels. Thus, elevated Ca^{2+} ion translocates from ER to

mitochondria which leads to ROS release and oxidative stress. Additionally, JNK inhibition was shown to suppress TEF-induced apoptosis. Therefore, this study reveals the apoptotic role of TEF against HCT-116 cell line via IRE1-α and mito-JNK pathway and inhibition of the major survival signalling pathways like the PI3K/Akt/mTOR and an induction of the pro-apoptotic JNK/JUN pathways (Refolo et al. 2015; Khan et al. 2016).

3.6 Conclusions and Future Prospects

Colon cancer is the second leading cause of cancer death, and out of the 140,000 people diagnosed with colon cancer each year in the USA, about 40% dies (Siegel et al. 2013). Treatment of CRC includes combination of surgery, radiation therapy, chemotherapy, and targeted therapy. If cancer cells are confined within the wall of the colon, it may be curable with surgical removal, while, when it has metastasized, it is usually not curable (Qi et al. 2010). However, depending on cancer condition and stages, all the cancer can be removed with surgery, and it also depends on persons overall health. Regular screening is recommended starting from the age of 50 to 75, for preventing and decreasing deaths from CRC. Initially, first-line chemotherapeutic agent oxaliplatin and/or 5-fluorouracil (5-FU) is the first choice for colon cancer treatment, which acts as a DNA synthesis inhibitor used for the CRC treatment (Cheng et al. 2017). If a large polyp or tumour is found, aspirin and other non-steroidal anti-inflammatory drugs are used to decrease the risk. Their routine use is not recommended for this purpose, however, due to side effects (Esther et al. 2010).

The anticancer effect of phytochemicals and its beneficial effects on cancer-related symptoms (e.g. fatigue, pain, vomiting, and anorexia) or on quality of life have been reported for their antitumour actions (Hosseini and Ghorbani 2015). In this chapter, we have focused overall beneficial effects of phytochemicals and mechanism of action of several types of herbal extracts against CRC. 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 include different organic constituents such as flavones, flavanols, isoflavones, catechins, EGCG, and epicatechins. Numerous plants are reported to have polyphenols in their extracts.

Nutraceutical is a term derived from nutrition and pharmaceutical and is sometimes termed ‘functional foods’. Nutritional phytochemicals have a strong historical background and significant applications in modern medicine. These compounds are used in medicinal and commercial industries for cosmetics, food aids, and additives (McCulloch et al. 2011; Palaniselvam et al. 2014). Previous seminal work has been summarized above, which demonstrates the key molecular mechanism of tumorigenes is inhibition by medicinal plants (Yaeger 2013). We have also outlined various mechanisms of EGFR inhibition (highly expressed in case of CRC) (Grossmann and Samowitz 2011) that are induced by naturally occurring chemopreventive

agents such as ginseng, green tea, and curcumin and describing its mechanism of action (Hamam 2014; Fujiki et al. 2015a; Pabla et al. 2015). Major advances in understanding of cell cycle regulation mechanisms provided a better knowledge of the molecular interactions involved in human cancer. Further mechanistic investigation is required to find out switches that connect common effector pathways that regulate cell behaviour, phenotype alteration, and cell death or lineage commitment. Human intervention studies of phytochemical, whether alone or in combination, are indicated against intermediate biomarkers and morphological stages of gastrointestinal tumorigenesis, thus providing a useful component of dietary or pharmacological treatment that aimed at reduction of the incidence and mortality from cancer (Khan and Mukhtar 2010).

We have reviewed on many evidences using cell culture model system, preclinical studies, and clinical trials (patients with CRC or at risk, familial adenopolyposis or aberrant crypt foci) investigating the protective mechanisms of phytochemicals and crude extract like curcumin, resveratrol, isoflavones, and green tea extracts (epigallocatechin gallate) (Table 3.6). From the data reviewed in this chapter, it can be concluded that these compounds inhibit cell growth, by inducing cell cycle arrest and/or apoptosis; inhibit proliferation, angiogenesis, and/or metastasis; and exhibit anti-inflammatory and/or antioxidant effects. Graphical overview of signal transduction pathway explains the role of herbal medicines in CRC (Fig. 3.1). In turn, these effects involve multiple molecular and biochemical mechanisms of action, which have been explained partially, still not completely characterized.

Table 3.6 Herbal medical plant extracts in treatment of CRC

Herbal composite	Plant source	Possible mechanism of anticancer CRC	References
Astragalus saponins (AST)	*Radix Astragali* (Huangqi)	Modulation of mTOR signalling, downregulates COX-2, VEFG	Law et al. (2012), Lopez-Sa´nchez et al. (2014), and Ran et al. (2016)
Ginsengs	Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*) Notoginseng (*Panax notoginseng)*	Antioxidants, cell cycle arrest, apoptosis, and inhibits angiogenesis	Li et al. (2009a, b), Zheng et al. (2013), Wang et al. (2014, 2015a, b, c), and Jin et al. (2016)
Mistletoe extracts	*Viscum album* (mistleotoe)	Cytotoxic, cell cycle arrest, apoptosis, and immune modulator	Harmsma et al. (2006), Horneber et al. (2008), and Ma et al.(2008)
(-)-Epigallocatechin gallate (EGCG)	Green tea (polyphenolic constituent)	Antioxidants, tyrosine kinase receptor inhibitor; inhibits cell proliferation, immune modulator, APC inducer, WNT/β--catenin, MAPK/Akt pathways	Jin et al. (2010), Fujiki et al. (2015a, b), Hu et al. (2015a, b, 2016), and Shin et al. (2017)

(continued)

Table 3.6 (continued)

Herbal composite	Plant source	Possible mechanism of anticancer CRC	References
Ganoderma lucidum extract (GLE)	*Ganoderma lucidum*	Inhibits DNA synthesis, cell cycle arrest, apoptosis via mitochondrial disruption	Xie et al. (2006), Qi et al. (2010), Oka et al. (2010), Liang et al. (2015), and Na et al. (2017)
Phyllanthin	*Phyllanthus watsonii*	Cytotoxicity, apoptotic effect	Ramasamy et al. (2012)
Curcumin	Turmeric (phytochemical)	Cell cycle arrest (p53 dependent and independent, cyclin dependent), inhibition of cell proliferation, apoptosis	Mao et al. (2007), Howells et al. (2010), and Shanmugam et al. (2015)
Resveratrol	Red grapes (phytoalexin)	COX-2, APC, NF-kB, cyclin D1, p53, apoptosis, miR-200c	Chen et al. (2012), Demoulin et al. (2015), Schroeter et al. (2015), Khaleel et al. (2016), Reddivari et al. (2016), Gong et al. (2017), and Karimi Dermani et al. (2017)
Betulinic acid (BA)	Barks of the plants	VEGF, ROS, DNA damage (NF-kB, p53), apoptosis	Alakurtti et al. (2006), Marcin et al. (2009), Ren et al. (2010), Mullauer et al. (2011), and Gomathi et al. (2014)
Silibinin, silymarin (crude form)	Milk thistle (a polyphenolic flavonoid)	Cell cycle arrest, cell proliferation, NF-kB, MMP2, p53, and apoptosis	Yang et al. (2005), Kaur et al. (2009), Kauntz et al. (2011), Lin et al. (2012), Wang et al. (2012), and Raina et al. (2013a)
Tanshinone	*Salvia miltiorrhiza Bunge* (diterpenes)	Inhibits VEGF, miR-155, TNF-alpha	Su et al. (2008a, b), Lee et al. (2012a, b), Hu et al. (2015a, b), Zhang et al. (2016), and Sui et al. (2017)
Quercitin	Fruits and vegetables (antioxidants, flavonoids)	JNK, p53, NF-kB, COX-2, cell cycle arrest, apoptosis	Fridrich et al. (2008), Atashpour et al. (2015), Refolo et al. (2015), Khan et al. (2016), Yang et al. (2016a, b), Raja et al. (2017), and Zizkova et al. (2017)

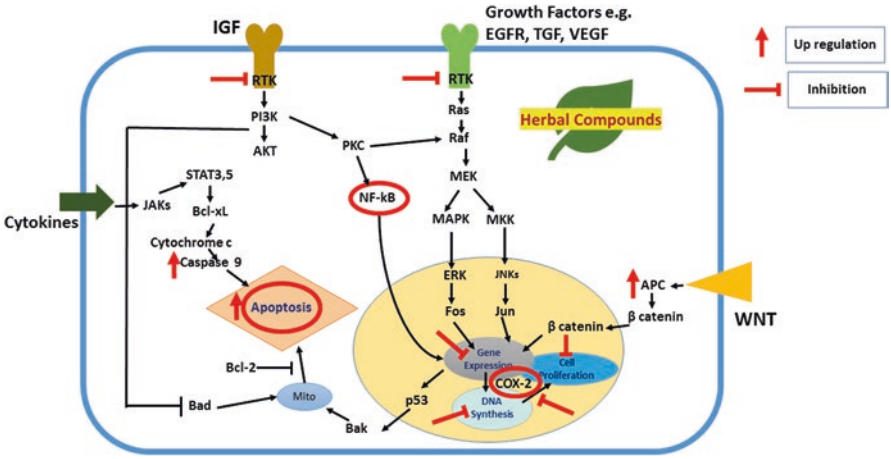

Fig. 3.1 Diagrammatic representation of signals transduction pathway. Black arrows and letters indicate regulators involved in signalling pathways and their components, while the herbal medicines targeting the pathway at different cellular level of the cascade are indicated in red colour as upregulators, inhibitors, and key regulators (circled)

Thus, caution is mandatory when attempting to extrapolate the observations obtained in CRC cell line studies to humans (Araújo et al. 2011). To date, chemopreventive properties of polyphenols are the most promising and potential future adjuvant in CRC management. Overall, the clinical evidence of mechanistic action of dietary phenolics against CRC is statically weak; still we have discussed here the possible reasons behind its mechanism of action as an antitumourigenic, anti-apoptotic, and anti-proliferative properties of compounds (Núñez-Sánchezet al. 2015). Moreover, if synergistic effects between herbal medicines and chemotherapy agents can be identified, reduction of chemotherapy dose in combination with herbs can further decrease dose-related drug toxicity and CRC. The identification of nontoxic anticancer herbal medicines remains as an essential step in advancing the treatment of cancer.

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