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Abstract

Worldwide, colorectal cancer (CRC) remains a major cancer type and leading cause of death. Unfortunately, current medical treatments are not sufficient due to lack of effective therapy, adverse side effects, chemoresistance and disease recurrence. In recent decades, epidemiologic observations have highlighted the association between the ingestion of several phytochemical-enriched foods and nutrients and the lower risk of CRC. According to preclinical studies, dietary phytochemicals exert chemopreventive effects on CRC by regulating different markers and signaling pathways; additionally, the gut microbiota plays a role as vital effector in CRC onset and progression, therefore, any dietary alterations in it may affect CRC occurrence. A high number of studies have displayed a key role of growth factors and their signaling pathways in the pathogenesis of CRC. Indeed, the efficiency of dietary phytochemicals to modulate carcinogenic processes through the alteration of different molecular targets, such as Wnt/β-catenin, PI3K/Akt/mTOR, MAPK (p38, JNK and Erk1/2), EGFR/Kras/Braf, TGF-β/Smad2/3, STAT1-STAT3, NF-κB, Nrf2 and cyclin-CDK complexes, has been proven, whereby many of these targets also represent the backbone of modern drug discovery programs. Furthermore, epigenetic analysis showed modified or reversed aberrant epigenetic changes exerted by dietary phytochemicals that led to possible CRC prevention

or treatment. Therefore, our aim is to discuss the effects of some common dietary phytochemicals that might be useful in CRC as preventive or therapeutic agents. This review will provide new guidance for research, in order to identify the most studied phytochemicals, their occurrence in foods and to evaluate the therapeutic potential of dietary phytochemicals for the prevention or treatment of CRC by targeting several genes and signaling pathways, as well as epigenetic modifications. In addition, the results obtained by recent investigations aimed at improving the production of these phytochemicals in genetically modified plants have been reported. Overall, clinical data on phytochemicals against CRC are still not sufficient and therefore the preventive impacts of dietary phytochemicals on CRC development deserve further research so as to provide additional insights for human prospective studies.

Keywords: Dietary phytochemicals; colorectal cancer; microbiota; molecular targets; signaling pathways; epigenetic regulators; preclinical study; clinical study.

Contents

1. General overview of colorectal cancer

1.1. Epidemiology and etiology of colorectal cancer

Globally, colorectal cancer (CRC) is the third most widespread cancer in both men and women, with more than 690000 deaths per annum (Ferlay et al., 2015). In developed countries (e.g.,Canada, Australia, United States, and European countries), the mortality rates are higher compared to developing countries (e.g., Africa, Central America, Japan, China, Singapore and Korea) in recent years (Siegel et al., 2016). On the global economy, CRC has a great impact on medical care. By 2020, CRC is estimated to exceed $17 billion in the healthcare system only in the USA (Mariotto et al., 2011).

CRC can develop through the mutation of specific genes related to a tumor suppressor gene, oncogene and DNA repair mechanism. About 70% of CRC cases occur sporadically due to transformation of specific morphological traits, starting from adenoma to carcinoma state, while 5% are related to inherited traits (hereditary non-polyposis CRC or Lynch syndrome, familial adenomatous polyposis (FAP) and MUTYH-associated polyposis) and the remaining 25% of CRC are associated with familiarity; only a few cases are known to be associated with high microsatellite instability (MSI), and with DNA mismatch repair deficiency (Li and Martin, 2016; Núñez-Sánchez et al., 2015). Several risk factors are strongly involved in

CRC progress, such as low levels of physical movement, obesity, diets with low fiber and high content of red meat or fat, cigarette smoking, alcohol abuse, environmental factors and intestinal dysbiosis (Gao et al., 2015; Huxley et al., 2009). Furthermore, a family history of CRC or chronic inflammatory bowel disease increases the incidence of Crohn's disease and ulcerative colitis, which contribute the CRC progression (Terzić et al., 2010).

1.2. Molecular targets in colorectal cancer

CRC is thought to occur as a result of genetic and epigenetic modifications in a range of genes promoting and enhancing MSI and chromosomal instability (CIN), and CpG island methylation (CIMP) (Boland and Goel, 2010; Lao and Grady, 2011; Pino and Chung, 2010). Most of the CRC occurs by CIN due to aneuploidy and loss of heterozygosity, which affects the number of genes associated with cell function, such as APC, Kirsten rat sarcoma virus oncogene (Kras), B-raf proto-oncogene (Braf), Tp53, etc. (Pino and Chung, 2010). Mutations of the APC gene can promote the dysregulation of β-catenin and therefore activate the wingless-type (Wnt) pathway, a common mechanism for initiating polyps to cancer progression (Vogelstein et al., 1988). Activated Wnt pathway promotes the expression of cellular Myc proto-oncogen (c-MYC) and the cyclin D1 gene, which induce favorable conditions for cancer cell growth (He et al., 1998). In addition, mutations of tumor suppressor genes (e.g., p53) and oncogenes (Kras or Braf) occur in approximately 55% to 60% of CRC and result in changes in cell propagation, apoptosis, cell cycle and DNA repair mechanisms (Rodrigues et al., 1990; Smith et al., 2002). The mitogen-activated proteins kinases (MAPKs), including extracellular signal-regulated kinases (Erk1/2), p38MAPK and Jun amino-terminal kinases (JNK), are known to communicate, enlarge and integrate signals from a wide variety of stimuli in controlling cellular proliferation, development, differentiation, inflammatory responses and apoptosis in CRC (Dhillon et al., 2007). Additionally, activated phosphatidylinositol 3-kinase (PI3K/Akt pathway) promotes tumor progression via suppression of apoptosis and promotion of the cell cycle (Vivanco and Sawyers, 2002). In CRC and colitis-associated tumors, nuclear factor-κB (NF-κB) activation

has also been identified and it regulates a number of genes accountable for the generation of pro-inflammatory mediators and cytokines (cyclooxygenase 2 (COX-2), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and IL1β) (Ohta et al., 2006; Wang et al., 2009), essential for the progression of CRC development.

Epidermal growth factor receptor (EGFR) is expressed in 60% to 80% of CRC (Goldstein and Armin, 2001), and has been related to several signaling pathways such as Kras-Braf-MEK-MAPKs and PI3K/Akt (Custodio and Feliu, 2013). Vascular endothelial growth factor (VEGF) is expressed in about 50% of CRCs and represents a vital angiogenic factor for CRC progression (Bendardaf et al., 2008). Moreover, activation and expression of matrix metalloproteinase (MMP)-2 and MMP-9 in CRC is related with cancer development, invasion, angiogenesis and metastasis (Mook et al., 2004). Transforming growth factor beta (TGF-β) signaling pathway has the potential to control a range of biological processes, and alterations in this pathway and promotes CRC cell growth, migration, invasion, angiogenesis and metastasis (Ramamoorthi and Sivalingam, 2014). Furthermore, insulin may promote CRC by enhancing the bioactive insulin-like growth factor (IGF)-1, either directly or via supression of IGF binding proteins that increase free IGF-1 (Grimberg and Cohen, 2000).

1.3. Current treatment and management of colorectal cancer

In the early stage, CRC can be diagnosed by several methods such as fecal occult blood testing, double-contrast bariumenema X-ray, flexible sigmoidoscopy and colonoscopy (gold standard) (Jenkinson and Steele, 2010). The common CRC biomarkers are metabolites, DNA, RNA or proteins for the detection of CIN, MSI, CIMP, Braf and Kras mutations in tumor specimens to classify the tumor stage or grade, providing a prediction of disease progression and therapy (Mármol et al., 2017). Currently, next generation sequencing (NGS) is also being implicated for CRC determination, such as DNA sequencing by ColoSeq™ assay for screening hereditary CRC, miRNA sequencing by RT-qPCR or miRNA microarray assay that can differentiate the healthy tissue from CRC tissue, while 16S rRNA sequencing can discriminate gut

microbiota composition in healthy and CRC tissue (Li and Martin, 2016). Also, a large number of kits for the determination of other gene expression profiles are under clinical investigation (Li and Martin, 2016). In general, tumor resection is carried out for the treatment of all stages of CRC. The application of different chemotherapeutics as neoadjuvants or adjuvants such as FOLFIRI and FOLFOX, along or in combination with bevacizumab, cetuximab, oxaliplatin, or panitumumab, relies on the patient's condition and the CRC stage (Schmoll et al., 2012). Of note, about 50% CRC patients will develop recurrent disease (Jemal et al., 2009), demonstrating that the currently existing treatments are unable to manage this deadly disease. The affordability and complexity issue jointly with high drug resistance percentage has augmented the difficulty of CRC treatment worldwide, thus immediate attention needs to focus on complementing the existing therapies. Moreover, the limitations of existing CRC treatment cytotoxic drugs are that they are insufficiently available or affordable in some regions (particularly in the least developing countries), and their application is also linked with a variety of unwanted and adverse effects.

2. Why phytochemicals?

Phytochemicals are non-nutritive secondary plant compounds often with health promoting and disease preventive properties, mainly found in fruits, vegetables, grain, herbs, spices and other plant foods. On the basis of epidemiological as well as preclinical and clinical research evidence, the consumption of fruits and vegetables exerts health-promoting effects against different types of tumors (González-Vallinas et al., 2013; Lee et al., 2011). About 70% to 90% of CRC are correlated with dietary factors, and diet optimization can avoid most of the cases (Ahmed, 2004; Shannon et al., 1996). A positive correlation between phytochemicals and CRC prevention has been noticed in several epidemiological studies (Fung et al., 2010; Nomura et al., 2008; van Duijnhoven et al., 2009) and in a number of studies aimed to investigate the anti-cancer effects of phytochemicals in CRC models (Afrin et al., 2016; Núñez-Sánchez et al., 2015; Ricciardiello et al., 2011). Therefore, there is a need to establish novel compounds that are non-toxic and that can be utilized in combination therapy to improve the response of cancer cells to chemotherapeutic

mediators. As a result, scientists have paid great attention to build up preventative strategies and treatments to decrease the incidence of CRC. The discovery of new potential phytochemicals with cancer preventive and therapeutic properties is based first on a screening assay for identifying specific affected molecular targets, next using validation techniques employing animal models or specific population targets, and eventually particular clinical trials which could be planned to study the targeted signaling pathways that are altered in particular types of cancer patients (Atanasov et al., 2015).

It has been found that phytochemicals can modulate key cellular signaling pathways by targeting different stages of CRC (initiation to progression) (Fig. 1), and research endeavors have centered on the roles of phytochemicals in signalling cascades that are presumed to induce chemopreventive activities (González-Vallinas et al., 2013; Lee et al., 2011). Therefore, this comprehensive review summarizes the most current information (PubMed and Google Scholar were searched for all original and review articles from 2012-2017 for preclinical studies and from 2004-2017 for clinical studies) of well-investigated dietary phytochemicals, mainly polyphenols, terpenoids and sulfur-containing compounds (Table 1) in CRC chemoprevention and their relation to intestinal microbiota. Particular attention has been paid to their molecular targets and epigenetic modification in *in vitro* and *in vivo* studies, as well as to the diverse clinical trials that have confirmed them to be potential therapeutic and chemopreventive agents.

3. Phytochemical metabolism in the colon and its relevance for colon cancer

Existing evidence indicates that the human intestinal microbiota (*Bacteroidesfragilis, Helicobacter hepaticus, Escherichia coli* strain NC101, *Fusobacterium*spp., *Campylobacter* spp. etc.) play a vital role in the aetiology of colon cancer, not only through the pro-carcinogenic actions of particular pathogens but also altering the immune function, tumor microenvironment through inflammation, or the metabolism of the host and stimulating the production of internal factors that have an effect on carcinogenesis (Gao et al., 2015). In recent investigations, hereditarily modified bacteria and their metabolites are taken into consideration, and some useful commensal bacteria are presently being experimented in some clinical cases

(Abreu and Peek, 2014). Moreover, it would be highly advantageous to introduce some dietary compounds or foods that could be applied to prevent CRC via their ability to modulate the intestinal microbiota.

It is increasingly recognized that natural compounds exert some of their important bioeffects on the body via complex interactions with the host´s microbiota (Eid et al., 2017; Espín et al., 2017). Dietary phytochemicals are bound to fiber or are mostly present as glycosides and complex molecules with less bioavailability and poor solubility (Bohn et al., 2015; Louis et al., 2014). Only limited accumulation appears in the small intestine and the structure and profile of most of the dietary phytochemicals are altered by bacterial fermentations in the large intestine, resulting in metabolites with more bioavailability and better pharmacological properties (Marín et al., 2015). The bioactivity of these metabolites can be changed by hydrogenation, dehydroxylation and demethylation. In addition, metabolites that are derived from microbial activities may be subjected to additional methylation, glucuronidation, glycination, or sulfation in the liver that promotes their distribution to tissues and excretion into the small intestine through bile (Bohn et al., 2015; Louis et al., 2014). Bacterial β-glucuronidases convert glucuronides to the aglycones that can be re-absorbed in the gut. Therefore, the activity of bacterial β-glucuronidase and the enterohepatic circulation have the potential to enlarge the retention time of phytochemicals in the human body (Bohn et al., 2015; Louis et al., 2014).

Growing evidence suggests that dietary phytochemicals are metabolized by the gut microbiota into active compounds (Table 1) that are able to i) enhance bioavailability, compared to the native compound (Ozdal et al., 2016), ii) decrease pathogenic microorganisms (Etxeberria et al., 2013), iii) avert colonic bacterial enzyme activities (Karthikkumar et al., 2012), iv) generate antioxidant effects (Louis et al., 2014), v) modulate xenobiotic detoxification pathways (Louis et al., 2014), vi) reduce oxidative DNA damage (Del Rio et al., 2013), vii) suppress pro-inflammatory mediators (Larrosa et al., 2009), viii) modulate cell proliferation and apoptosis (Del Rio et al., 2013; Ramos, 2008), ix) target key carcinogenic pathways (Del Rio et al., 2013; Ramos, 2008) and x) elevate the prebiotic function of the dietary fibers (Dethlefsen et al., 2006).

4. Molecular targets of dietary phytochemicals for colorectal cancer prevention: preclinical studies

Using *in vitro* and *in vivo* models, dietary phytochemicals have been implicated in an extensive range of anticancer activities: anti-proliferation, cell-cycle blockage, DNA repair alteration, apoptosis induction, anti-inflammation, activation of tumor-suppressor genes and suppression of oncogenes, regulation of the levels of hormonal and growth-factors, and inhibition of invasion, angiogenesis and metastasis (Table 2).

4.1. Polyphenols

Polyphenols are a very diverse and multifunctional group of bioactive compounds. These molecules are secondary metabolites of plants, biosynthesized mainly for defense against oxidative damage and stress and generally display a substantial health-improving potential in many areas (Braicu et al., 2017; Cătană et al., 2018; Tewari et al., 2018). In the human diet there are approximately 8,000 different polyphenols from edible plants (Fraga et al., 2010), classified into different groups. Within them, the most important groups are phenolic acids, flavonoids, stilbenes, lignans and curcuminoids. This last decade has seen a remarkable increase in research on polyphenols, thanks to their antioxidant effects and to their ability to interact with cellular enzymes and receptors, thus modulating many molecular mechanisms involved in different biological functions (Pandey and Rizvi, 2009).

4.1.1 Flavonoids

4.1.1.1. Quercetin

Quercetin is synthesized from three molecules of malonyl CoA, derived from the metabolism of fatty acids, and one of p-coumaroyl CoA, synthesized from phenylalanine via the general phenylpropanoid pathway in a reaction catalysed by chalcone synthase (CHS). The product of this reaction is naringenin-chalcone. The next step in this flavonoid biosynthesis pathway is the stereospecific conversion of naringenin-chalcone to naringenin by chalcone isomerase (CHI). The enzyme flavanone 3-hydroxylase (F3’H) catalyzes the

hydroxylation at C3 with the conversion of naringenin to dihydrokaempferol. The subsequent steps involve the introduction of a Δ2,3 double bond to convert dihydrokaempferol to the flavonol kaempferol, and then flavonol 3-hydroxylase is responsible for the synthesis of dihydroquercetin. Finally, flavonol synthase (FLS) converts dihydroquercetin to quercetin (Crozier et al., 2006).

In plants, quercetin and its derivatives mainly occur in leaves and in the outer parts of the plants in the form of aglycones and glycosides, in which one or more sugar groups are bound to the phenolic groups by glycosidic bonds. Onions, for example, are a particularly rich source of quercetin glucosides. Yellow onions are one of the main sources of these flavonols, with the edible flesh containing between 280 and 490 mg/kg. Makris and Rossiter (2001) also detected 280 mg/kg of quercetin-3-O-rutinoside in fresh asparagus. Tomatoes also contain flavonols, mainly in the form of quercetin-3-O-rutinoside, which accumulates in the skin, with cherry tomatoes being an especially rich source due to their high skin to volume ratio (Stewart et al., 2000). Quercetin is abundant in mulberries (359.4 mg/kg-1), apricots (322.1 mg/kg-1), and apples (119.5 mg/kg-1) (Sultana and Anwar, 2008).

Quercetin and its derivatives exert growth inhibitory effects in colon cancer by reducing tumor growth and suppressing cell survival or proliferation rate through the induction of apoptosis or autophagy and arresting cell cycle by modulating different molecular targets. A huge number of studies have addressed the apoptotic effect of quercetin in several models of CRC cells highlighting a decrease in the expression of MYC, B-cell lymphoma (Bcl)-2, Bcl-xl and at the same time an enhancement in the expression of p53, caspase-3, -9, cleaved Poly (ADP-ribose) polymerase (c-PARP) (Kee et al., 2016; Refolo et al., 2015; Yang et al., 2016; Zhang et al., 2015), as well as a reduced mitochondrial membrane potential (MMP) (Cincin et al., 2015; Khan et al., 2016; Kim, G.T. et al., 2014). Furthermore, it stimulated MAPK pathways, including p38MAPK, JNK and Erk signaling for the induction of cancer cell death by stimulating apoptosis (Fig. 2) (Kee et al., 2016; Refolo et al., 2015; Yang et al., 2016; Zhang et al., 2015). In DLD-1 colon cancer cells, quercetin activated p38MAPK, which further activated caspase-3 and cleavage of PARP protein (Bulzomi et al., 2012). Interestingly, quercetin-induced apoptotic death of colon cancer HT-29 and HCT-116 cells by

modulating AMP-activated protein kinase/mechanistic target of rapamycin (AMPK/mTOR) (Kim, G.T. et al., 2013) and AMPK/p38 (Kim, G.T. et al., 2014) pathway which triggered sirtuin 2 (SIRT-2) expressions in a p53-independent way and also induced intracellular reactive oxygen species (ROS) generation (Kim, G.T. et al., 2014; Kim, G.T. et al., 2013). In hypoxic conditions, it inhibited AMPK expression by reducing hypoxia inducible factor-1 (HIF-1) activity (Kim et al., 2012) and the result was also confirmed in an *in vivo* CRC model (Kim et al., 2012).

5,30-dihydroxy-3,7,40-triethoxyflavone (TEF) is a quercetin derivative that induces apoptotic death of colon cancer HCT-116 cells by endoplasmic reticulum (ER)-arbitrated apoptosis by increasing the inositol requiring kinase 1-α (IRE1-α) and X-box-binding protein 1 (XBP-1) protein expressions, which elevate intracellular Ca^{2+}, ROS and B-cell lymphoma 2 associated X (Bax) protein, and at the same time reduce Bcl-2 levels (Khan et al., 2016). Furthermore, TEF treatment decreased the ER stress downstream regulating protein, activating transcription factor (ATF)-6, protein kinase-like ER kinase (PERK), CCAAT-enhancer-binding homologous protein (CHOP), glucose-regulated protein-78 (GRP78) and p-eukaryotic initiation factor 2 alpha (p-eIF2α/ eIF2α) expression, and activated the JNK and p38 signaling pathways (Khan et al., 2016).

The anti-inflammatory effects of quercetin were observed in the suppression of toll like receptor (TLR) 4, NF-κB and other inflammatory factors (IL-6, COX-2 and TNF-α) expression in Caco-2 cells (Fig. 3) (Han et al., 2016). Furthermore, the expression of proliferation markers, phosphoglycogen synthase kinase 3-β (p-GSK-3β), p-PI3K/Akt, p-S6, p-eukaryotic translation initiation factor 4E-binding protein 1 (4EBPI) and p-signal transducer and activator of transcription (STAT3) decreased in DLD-1 and Caco-2 cells by inducing endocannabinoid receptor expression (Refolo et al., 2015). Additionally, suppressed Wnt/β-catenin in DLD-1 and Caco-2 (Refolo et al., 2015), Akt-CSN6-MYC in HT-29 (Yang et al., 2016) and NF-κB in Caco-2 and SW-620 (Zhang et al., 2015) cells were also observed after quercetin treatments. In HT-29 CRC cells, quercetin suppressed cell survival rate, which was associated with COX-2 dependent ROS generation and suppressed p-Akt and p-GSK-3β expression (Raja et al., 2017). Furthermore, quercetin or

its derivatives suppressed cell progression by blocking the cell cycle at G0/G1 (Kim et al., 2012; Yang et al., 2016) and G2/M phase (Fig. 4) (Enayat et al., 2016; Zhao, Y. et al., 2017). In a xenograft model of colon cancer, ingestion of quercetin reduced tumor volume and increased the survival rate (Hashemzaei et al., 2017).

A derivative of quercetin (isoquercitrin) suppressed the growth of colon cancer HCT-116, DLD-1 and SW-480 cells through the suppression of the Wnt/β-catenin signaling pathway by acting on the nuclear translocation of β-catenin (Fig. 5) (Amado et al., 2014). Analogous effects were also exerted in a functional model of *Xenopus* embryos (Amado et al., 2014). Interestingly, quercetin derivatives, 8-C-(E-phenylethenyl) quercetin (8-CEPQ) and 2-Chloro-1,4-naphthoquinone (CHNQ) induced autophagic cell death by i) increasing ROS generation in HT-29 and HCT-116 cells (Enayat et al., 2016), ii) accumulating acidic vesicle and autophagic vacuoles, iii) increasing puncta formation, iv) modulating Beclin-1 activity, v) increasing LC3-I and LC3-II expression, and vi) reducing expression of autophagic substrate, SQSTM1/p62 in SW-620, HT-29 and HCT-116 cells (Enayat et al., 2016; Zhao, Y. et al., 2017), p-Akt/PI3K in HT-29 and HCT-116 cells (Enayat et al., 2016), as well as increasing the expression of autophagy related gene 7 (ATG7) in SW-620 cells (Zhao, Y. et al., 2017), p-Erk1/2, p-p38 MAPK and p-JNK in SW-620, HT-29 and HCT-116 cells (Enayat et al., 2016; Zhao, Y. et al., 2017) .

Quercetin suppressed the metastatic ability of CT26 colon cancer cells through the regulation of the epithelial mesenchymal transition (EMT) by suppressing the expression of N-cadherin, β-catenin, and snail and increasing the expression of E-cadherin (Kee et al., 2016). Anti-invasive and anti-migratory activities were observed by decreasing cell migration ability in HT-29, CT26 and Caco-2 cells (Han et al., 2016; Kee et al., 2016; Refolo et al., 2015) and inhibiting the expression of MMP-2 and MMP-9 expression in HT-29 and CT26 cells after quercetin treatments (Han et al., 2016; Kee et al., 2016). Moreover, in a colorectal lung metastasis mouse model, intake of quercetin significantly decreased tumor nodules and lung weight (Kee et al., 2016).

4.1.1.2. Anthocyanins

Anthocyanins (water-soluble vacuolar pigments, plentiful in the skin of red grapes) are produced by a different branch of the flavonoid biosynthetic pathway; the enzymes CHI, F3'H, dihydroflavonol 4-reductase and anthocyanidin synthase (ANS, also known as LDOX) are required to synthesize anthocyanidin (pelargonidin). However, most plants further hydroxylate the B-ring using either the enzyme F3'H which forms cyanidin, or the enzyme flavonoid 3'5' Hydroxylase (F3'5'H) which forms delphinidin. Differences in the hydroxylation of the B-ring confer variations in the colour ranges of anthocyanidins, pelargonidin being orange to red, cyanidin red to red-purple and delphinidin being red-purple to blue depending on various other factors. The anthocyanidin structure is unstable and these pigments accumulate exclusively as glycosylated forms (anthocyanins) in nature, with carbon 3 linked to a glucose sugar residue through an oxygen molecule (Zhang et al., 2014). Most of the red, purple, and blue-colored plants, fruits and flowers contain anthocyanins. Burns et al. (2000) studied the range concentrations of phenolic compounds in 15 red wines of different geographical origins, and found a range of free and polymeric anthocyanins between 41 and 150 mg/L. Numerous varieties of plums (*Prunus domestica* L.) are cultivated world-wide and are a rich source of anthocyanins in the form of cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside, which are also found in peaches. Red onions, like their yellow counterparts, contain up to 250 mg/kg anthocyanins while rhubarb (*Rheum rhaponticum* L.) has 2000 mg/kg of anthocyanin (Crozier et al., 2006).

Anthocyanins induce chemopreventive effects, including anti-inflammation, anti-proliferation, apoptosis induction, cell cycle regulation, anti-invasion and anti-angiogenesis activities. Anthocyanin and anthocyanidin rich extract from plant sources induced apoptotic cell death by increasing c-PARP, caspase-3 and Bax/Bcl2 ratio in COLO 320DM cells (Hsu et al., 2012) and decreasing survivin, X-linked inhibitor of apoptosis protein (XIAP) and cellular inhibitor of apoptosis-2 expressions in HT-29 cells (Mazewski et al., 2018). Furthermore, anthocyanins containing potato extract killed colon cancer stem cells (CSCs) in CRC cells and animal models by inducing mitochondria-mediated apoptosis (elevating Bax and cytochrome

c) and disrupting the Wnt signaling by suppressing β-catenin and its downstream proteins c-MYC and cyclin D1 expressions (Fig. 5) (Charepalli et al., 2015). The accumulation of p27 and p21 and the decrease of cyclin E and cyclin D after the extract treatment of COLO-320DM and HT-29 cells may be accredited to the molecular mechanisms underlying the transition of the cells into G0/G1 phase arrest (Fig. 4) (Hsu et al., 2012). Furthermore, anthocyanin metabolites suppressed colon cancer Caco-2 cell growth by inhibiting the pro-oncogenic signals, such as AP-1, NF-kB and STAT-1 activity (Fig. 7) and blocking the cell cycle at G0/G1 phase (Forester et al., 2014). In addition, elevation of caspase-3 was also observed in HT-29 cells after treatment with strawberry and anthocyanin-rich grape extracts and their microbial metabolites (López de las Hazas et al., 2016).

Anthocyanin extracts from cocoplums (*Chrysobalanus icaco* L.) suppressed HT-29 cell proliferation by increasing ROS generation, and exerting also anti-inflammatory effects by suppressing the inflammation markers NF-κB1, TNF-α, IL-6 and IL-1β expression (Fig. 5) (Venancio et al., 2017). In the azoxymethane (AOM)-treated mouse model of colon cancer, anthocyanins inhibited the formation and growth of colon cancer by reducing inflammation (Lippert et al., 2017). Anthocyanins suppressed the invasion ability partially through the inhibition of cladin-3 via activation of p38-MAPK and the suppression of the expressions MMP-2 and MMP-9, which was arbitrated by the downregulation of PI3K/AKT signaling pathway in colon cancer HCT-116 cells (Fig. 6) (Shin et al., 2011).

Proanthocyanidins from different berries activated apoptosis increasing p-p38MAPK and caspase-8 in colon cancer SW-480 and SW-620 cells (Minker et al., 2015). At the intestinal lumen, hexameric procyanidins prevented bile-acid-induced activation of oncogenic signals (p38, Erk, Akt, and activator protein-1 (AP-1)) (Fig. 2 and Fig. 6) and NADPH oxidase activation, calcium mobilization, and oxidant production in Caco-2 colon cancer cells (Da Silva et al., 2012). Grape seed proanthocyanidins induced anti-angiogenic activity in SW-620 human colon cancer cells and colon tumor xenografts (chick chorioallantoic membranes) by inhibiting both VEGF and angiopoietin 1 expression through scavenging ROS (Huang et al., 2012).

4.1.1.3. Genistein

Genistein, the predominant isoflavone of soybeans, is biosynthetically the simplest of isoflavonoid compounds found in Leguminosae. It is a central intermediary in the biosynthesis of more complex isoflavonoids with roles in the establishment or inhibition of interactions between plants and microbes (Dixon and Ferreira, 2002). To enter the isoflavonoid pathway, the flavanone first undergoes abstraction of a hydrogen radical at C-3 followed by B-ring migration from C-2 to C-3 and subsequent hydroxylation of the resulting C-2 radical. This reaction, catalyzed by a microsomal cytochrome P450 enzyme, requires NADPH and molecular oxygen to convert naringenin and isoliquiritigenin into the isoflavones genistein and daidzein respectively (Dixon and Ferreira, 2002). These isoflavonoids enjoy a restricted distribution in the plant kingdom, as they are limited to the subfamily Papilionoideae of the Leguminosae. The levels of these isoflavones in soybeans have been reported to range from 560 to 3810 mg/kg (Fielden et al., 2003).
Genistein has received much attention because of its efficientanti-carcinogenic effects and probable function in various signaling pathways in CRC. Chemopreventive activity of genistein or its derivative (GEN-27) may constitute an important determinant in the inhibition of colon cancer progression both in *in vitro* and *in vivo* models by inhibiting the Wnt/β-catenin signaling pathway (Fig. 5) (Du et al., 2016; Lepri et al., 2014; Sekar et al., 2016; Zhang, Y. et al., 2013). Increased APC level and axis inhibition protein 2 (AXIN2) expression were observed, while the expressions of p-GSK-3β levels (Du et al., 2016) and β-catenin target genes, including proliferating cell nuclear antigen (PCNA), cyclin D1 and c-MYC, were found to be lowered after treatment with this phytochemical (Du et al., 2016; Wang, Y. et al., 2016; Zhang, Y. et al., 2013). Moreover, genistein induced anti-proliferative activity through downregulation of EGFR in HCT-116 (Gruca et al., 2014) and p38 MAPK in HT-29 (Fig. 2) (Shafiee et al., 2016) cells. Apoptotic cell death by genistein treatment associated with inhibited NF-κB pathway, as well as downregulated Bcl-2 (Luo et al., 2014; Wang, Y. et al., 2016) and upregulated Bax (Luo et al., 2014) expressions, were

observed, while caspase-3 (Shafiee et al., 2016) and ROS increased and mitochondrial membrane potential (MMP) (Wu et al., 2017) was reduced in colon cancer cells.

GEN-27 suppressed inflammation-induced HT-29, HCT-116 and SW-620 colon cancer cells proliferation by inhibiting NF-*κ*B signaling (Fig. 3) (Du et al., 2016; Wang, Y. et al., 2016). In chemically induced *in vivo* CRC model, genistein or GEN-27 induced therapeutic effects by suppressing the nuclear translocation of NF-κB/p65 and inhibiting expression of the inflammatory cytokine TNF-α, IL-6 and IL-1β (Fig. 3) (Du et al., 2016). In an *in vivo* colon carcinogenesis model, genistein exhibited anti-cancer effects by activating nuclear related factor 2 (Nrf-2) and its downstream target HO-1 and decreasing the expressions of proliferative (PCNA) and CSC (CD133, CD44) markers (Sekar et al., 2016).

Furthermore, genistein suppressed cell growth by blocking the cell cycle at G0/G1 (Du et al., 2016; Wang, Y. et al., 2016) and G2/M phase (Han et al., 2013; Mizushina et al., 2013; Wu et al., 2017; Zhang, Z. et al., 2013), with a significantly decreased cyclin B1, serine/threonine-proteinkinase 2 (Chk2) (Han et al., 2013), cell division cycle (cdc)2 and cdc25A expression, and increased activation of ATM/p53, p21waf1/cip1 and DNA damage-inducible gene 45α (GADD45α) (Zhang, Z. et al., 2013) in several colon cancer cells (Fig. 4). Anti-metastatic activity of genistein was also associated with suppressed expression of MMP-2 (Shafiee et al., 2016; Xiao et al., 2015), Fms-related tyrosine kinase 4 and CD34, concurrent with inhibiting cell migration and invasion ability both in *in vitro* and *in vivo* experimental colon carcinogenesis (Xiao et al., 2015).

4.1.1.4. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is produced via the naringenin-chalcone − naringenin − dihydrokaempferol pathway (Ashihara et al., 2010). The reactions leading to the synthesis of dihydromyricetin are catalyzed by the following enzymes: phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (C4H), CHS, CHI, F3’H and flavonol 3'5-hydroxylase which catalyze hydroxylation at C3 and C5. Epigallocatechin (EGC) is formed in steps involving sequential reactions catalyzed by

leucoanthocyanidin 4-reductase, ANS, and anthocyanidin reductase. Finally, EGC is converted into EGCG (esterified catechin) via the sequential action of flavan-3-ol gallate synthase (Liu et al., 2015). The principal source is green tea, which contains 7380 mg/100 g, while white tea contains 4245 mg/ 100 g, and black tea even smaller quantities (936 mg/100g). Trace amounts are found in apple skin, plums, onions, hazelnuts, pecans, and carob powder (109 mg/100 g) (Crozier et al., 2006).

EGCG has been reported to exert anti-cancer effects against different cell line models of CRC by modulating multiple signaling pathways. In a panel of colon cancer cells, EGCG inhibited cell proliferation by suppressing Wnt/β-catenin (Fig. 5) (Oh et al., 2014) and PI3K/Akt (Fig. 6) (Kumazaki et al., 2013) signaling pathways, and inducing apoptosis by activating both p53-dependent and p53-independent pathways (Park et al., 2013). For example, increasedc-PARP and caspase-9 expression (Kumazaki et al., 2013), and activated MAPK (p-Erk1/2,p-p38MAPK and p-JNK1/2) target signaling (Fig. 2) (Cerezo-Guisado et al., 2015) were highlighted. Additionally, EGCG suppressed proteinase-activated receptor 2 (PAR2)-activating peptide-or factor VII-induced proliferation and migration ability by blocking the activation of NF-κB and Erk1/2 signaling and at the same time neutralizing the suppressed activity of caspase-7, elevated activity of tissue factor and MMP-2 (Zhou et al., 2012). In APC mutated colon cancer cells, EGCG suppressed cancer cell growth through the inhibition of Wnt/β-catenin by stimulating the phosphorylation and proteasomal degradation of β-catenin via a system independent of the GSK-3β and protein phosphatase 2A and repressing cyclin D1 and c-MYC expression (Fig. 5) (Oh et al., 2014).

Synergistic effect of EGCG was observed when it was combined with other phytochemicals in CRC cells. In Caco-2 and LoVo cells, when EGCG was combined with raphasatin and vitexin-2-O-xyloside, it enhanced effectiveness by arresting the cell cycle at G0/G1 phase and inducing mitochondrial reliant apoptosis by activating Bax, caspase-9 and PARP, and decreasing Bcl-2 expression, as well as increasing ROS generation (Papi et al., 2013). Furthermore, combination treatment of EGCG and sodium butyrate (dietary microbial fermentation product of fiber) was more efficient in stimulating apoptosis, cell cycle arrest and DNA-damage in CRCHT-29, RKO and HCT-116 cells (Saldanha et al., 2014). The effects were

principally correlated to the arrest of cell cycle at G1 and G2/M phase, the decrease of survivin through p21 induction and the increase of p53 expression (Fig. 4) (Saldanha et al., 2014).

EGCG treatment inhibited SW-620 cell invasion by decreasing the activity of MMP-9 (Zhou et al., 2012). In HT-29 and HCT-116 cells, EGCG suppressed the migration ability by reducing the expression of MMP-9 and VEGF (Park et al., 2013). Additionally, peracetylated(-)-epigallocatechin-3-gallate (AcEGCG) showed much more potency compared to natural EGCG for preventing chemically induced colitis and CRC in mouse model (Chiou et al., 2012). AcEGCG acted at different levels and induced epigenetic alteration by specifically elevating acetyl-Nrf2, activating Erk1/2 signaling, thereby resulting in the increase of antioxidant enzyme (HO-1) expression and inhibition of PI3k/Akt/NFκB activation, p65 acetylation, and COX-2, iNOS, TNF-α, IL-6 and IL-1β expressions (Chiou et al., 2012).

4.1.1.5. Kaempferol

The biosynthetic pathway for kaempferol has been identified in various plants. Initially, phenylalanine is converted into p-coumaryl-CoA by PAL, C4H and 4-coumaric acid ligase. Then, naringenin is generated through a condensation reaction between one molecule of p-coumaryl-CoA and three molecules of malonyl-CoA by CHS and CHI. Finally, naringenin is converted into kaempferol via dihydrokaempferol by flavanone 3β-hydroxylase and FLS (Duan et al., 2017). Kaempferol is mostly found in fruits such as apples, grapes and tomatoes and in plants such as green tea, pine, *Angelica decursiva* (Miq.) Franch. & Sav. and ginkgo (*Ginkgo biloba*L.) leaves (Kim and Choi, 2013). Kaempferol is the most abundant flavonol (9–23 mg/kg) in blackcurrants (Crozier et al., 2006).

Kaempferol has been shown to exert chemopreventive effects mostly by suppressing cell growth, inducing apoptosis and arresting cell cycle in *in vitro* CRC model. The mechanism was initiated by i) downregulating the expression of PI3K/Akt and Erk1/2 pathways by inhibiting IGF-IR and ErbB3 signaling (Fig. 2 and Fig. 6) (Lee et al., 2014a), ii) increasing cleaved caspase-9, -3, -7 and -8 as well as PARP activity, iii) increasing membrane-bound first apoptosis signal ligand (FasL), cytosolic cytochrome c concentrations and

mitochondrial membrane permeability, iv) decreasing the levels of Bcl-xL proteins, but increasing the levels of Bik and Bad (Lee et al., 2014b), and v) arresting cell cycle at G1 and G2/M phase through inhibiting the expression of CDK2, CDK4, cdc25C, cdc2, cyclin B1 cyclins D1, cyclin E, cyclin A and p-Rbproteins (Fig. 4) (Cho and Park, 2013). Kaempferol supplementation in a mouse CRC model induced protective effects against oxidative damage by decreasing liver thiobarbituric acid reactive substances (TBARS) level and rejuvenating anti-oxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) activities (Nirmala and Ramanathan, 2011).

4.1.1.6. Silibinin

In nature, silybin, a flavonolignan, occurs in the form of two trans diastereoisomers, A and B, which are differentiated by reference positions C-10 and C-11 in the 1,4-benzodioxane ring. Silibinin is produced by oxidative coupling between a flavonoid (taxifolin) and coniferyl alcohol (a phenylpropanoid). The enzyme CHS catalyzes the addition of a cinnamoyl-CoA unit to three malonyl-CoA units and the subsequent cyclization, giving chalcones. Hydroxylation of the two aromatic rings occurs at the flavanone or dihydroflavonol stage. Coniferyl alcohol is derived from reduction of cinnamic acid by a NADPH dependent reaction using coenzyme A. This is followed by aromatic hydroxylation and methylation. The oxidative coupling reaction between taxifolin and coniferyl alcohol is mediated by formation of free radicals and catalyzed by peroxidase enzyme (Dewick, 2002).

Silibinin has been recently investigated for its chemopreventive activity on CRC *in vitro* and *in vivo* experimental models. Silibinin induced apoptotic cell death in primary and TNF-related apoptosis-inducing ligand (TRAIL) resistance metastasis SW-480 and SW-620 cancer cells, by targeting both extrinsic pathway through the regulation of death receptors (DR)4/DR5 and caspase-8 and -10, and intrinsic pathway by disruption of the MMP, releasing cytochrome c into the cytosol and activating caspase-9 (Kauntz et al., 2012a). Additionally, silibinin and TRAIL synergistically induced mitochondrial apoptosis by decreasing of the expression of anti-apoptotic proteins myeloid cell leukemia 1 (Mcl-1) and XIAP (Kauntz et al.,

2012a). Furthermore, when silibinin was combined with regorafenibit, it exerted synergistic effects in a panel of colon cancer cell lines by inducing anti-proliferative effects through the inhibition of PI3K/Akt/mTOR signaling (Fig. 6) and the increase of intracellular ROS production levels (Belli et al., 2017). In order to improve the pharmacological properties of silibinin, it was combined with oxidovanadium (IV) complexes and the combination was more effective in inducing inhibitory effects on HT-29 cell growth by depletion of glutathione, induction of apoptosis by increased caspase-3, inhibition of inflammation by suppression of the NF-kB pathway (Fig. 3) and inhibition of topoisomerase IB activity (León et al., 2015). Moreover, silibinin and metformin combination enhanced in the growth rate of colon cancer COLO-205 cells by reducing p-Akt and p-mTOR, and increasing p-AMPK expression, and finally inducing apoptosis by increasing caspase-3 and apoptosis inducing factors (AIF) expression (Tsai et al., 2015).

In p53 wild and null type CRC HT-29 cells, silibinin induced apoptosis through early growth response-1-provoked up-regulating of non-steroidal anti-inflammatory drug-activated gene-1 expression, which was associated with increased ROS generation, p38MAPK signaling, and c-PARP expression (Woo et al., 2014). Furthermore, silibinin inhibited interleukin (IL-4 or IL-6)-induced pro-tumorigenic signals STAT3 (Fig. 7) and NF-κB (Fig. 3) expression in CSC enriched colon spheres (Kumar et al., 2014), and suppressed migration and invasion ability through the reduction of MMP-2 expression by attenuating the activity of JNK/AP-1 pathway in LoVo cancer cells (Lin et al., 2012).

In vitamin D-resistant colon cancer HT-29 cells, silibinin suppressed the effects of TNF-α-mediated Snail1 and Snail2 over-expression, increased vitamin D receptor expression, and renovated the anti-proliferative and anti-migratory effects of 1,25-dihydroxyvitamin D; these results are very promising since the levels of vitamin D receptors are reduced in both the inflamed colon and in CRC and are inversely associated with the epithelial/mesenchymal transition, thus representing a favorable prognostic indicator in CRC (Bhatia and Falzon, 2015). This phytochemical inhibited CSC self-regeneration and sphere formation in spheroid

culture by suppressing the activation of the AktSer473/mTOR signaling pathway via down-regulating the activity of protein phosphatase 2Ac subunit (PP2Ac) (Wang, J.Y. et al., 2012).

In rodent CRC model, silibinin exhibited diverse protective and anti-carcinogenic effects on the colonic mucosa at the pre-initiation stages. It decreased aberrant crypt foci (ACF) proliferation and formation, inhibited pro-inflammatory mediators such as MMP-7, IL1β and TNF-α, and induced apoptosis by decreasing Bcl-2 and increasing Bax expression (Kauntz et al., 2012b). Additionally, silibinin decreased inflammation, mucin degradation and adenoma formation in the dimethylhydrazine (DMH) induced rat colon by elevating the level of intestine-specific tumor suppressor gene caudal type homeobox 2 activity (Sangeetha and Nalini, 2015). In Apc−/+ mice model, silibinin decreased the progression of intestinal adenoma by blocking cell cycle entry, and induced apoptosis by targeting cyclin dependent kinase (CDK) pathway (CDK4, cyclin D1, and p-retinoblastoma (Rb)) (Fig. 4) (Karim et al., 2013). Additionally, ingestion of silibinin exerted chemopreventive activity in *in vivo* CRC model by inhibiting the tumorigenecity and tumor growth of cancer stem-like cells (Wang, J.Y. et al., 2012). Finally, the intratumoral injection of silibilin, coated with poly-(organophosphazene) gel in the xenografted CRC mice model, exhibited a good antitumor effect by decreasing VEGF expression in colon tissue (Cho et al., 2012).

4.1.2. Phenolic acid and derivatives

4.1.2.1. Gallic acid

The biosynthesis of gallic acid (GA), a trihydroxybenzoic acid originating in the shikimate pathway, starting with 3-deoxy-D-arabino-heptulosonate 7-phosphate synthase (DAHP) catalyzes an aldol-like reaction between phosphoenolpyruvate and D-erythrose 4-phosphate to produce chorismite. Elimination of phosphoric acid from DAHP generates the intermediate 3-dehydroquinic acid, which is converted into shikimic acid by dehydration and reduction steps. GA is formed directly from the dehydrogenation of shikimic acid by shikimate dehydrogenase (SDH) (Dewick, 2002). GA occurs in clove buds (*Eugenia caryophyllata* Thunb.) (175 mg/kg), green tea (6 mg/kg−1), and red wine (8–71 mg/L). Red fruits such as

strawberries, raspberries and blueberries, black tea, red wine and nuts are the main dietary sources (Crozier et al., 2006).

Gallic acid, a trihydroxybenzoic acid, inhibited cell proliferation and survival rate in part, by i) inhibiting transcription factors AP-1, NF-kB, STAT1 (Fig. 7), and OCT-1 expression in Caco-2 cells (Forester et al., 2014), and suppressing Wnt/β-catenin signaling (Fig. 5) in HCT-116 cells (Lee et al., 2016), ii) arresting cell cycle at G0/G1 phase through the decrease of cyclin D1 level (Fig. 4) and iii) inducing apoptosis by activating caspase-3 expression in Caco-2 cells (Forester et al., 2014), increasing ROS generation and decreasing MMP in HCT-15 cells (Subramanian et al., 2016). Additionally, GA induced the differentiation of CSCs and self-renewal capacity through down-regulation of the expression of the CSC markers, CD133, CD44, DLK1 and Notch1 in HCT-116 cancer cells (Lee et al., 2016). In chemically-induced colitis in mice, GA suppressed the expression level of inflammatory markers such as IL-6, COX-2, and iNOS and the degradation of the inhibitory protein IκB (Fig. 3) (Pandurangan et al., 2015). Additionally, it reduced the activation and nuclear accumulation of p65-NF-κB and p-STAT3Y705 in colonic mucosa (Pandurangan et al., 2015).

4.1.2.2. Ellagic acid

The exact origin of ellagic acid (EA), which is found in relatively low amounts in plant tissues, is unclear. Rather than being produced directly from gallic acid, it may be derived from ellagitannins, which liberate hexahydroxydiphenoyl residues upon hydrolysis in the form of free hexahydroxydiphenic acid, which undergoes spontaneous conversion to EA. EA is a hydroxybenzoate which has been reported to be present in berries, particularly raspberries (5.8 mg/kg), strawberries (18 mg/kg) and blackberries (88 mg/kg) (Crozier et al., 2006).

Ellagic acid, a naturally occurring flavonoid, exhibits chemopreventive effects in the line of itsanti-proliferative and pro-apoptotic activities, as well as its potentiality in modulating signaling pathways. In a gene expression profile assay, 857 differentially expressed genes were evaluated after EA treatment in colon

cancer cells. According to the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, a significant number of molecular targets were altered after EA treatments that were related with cell proliferation, apoptosis, cell cycle arrest and angiogenesis (Zhao, J. et al., 2017). EA induced growth inhibitory effects through the suppression of PCNA, cyclin D1, PI3K/Akt and Kras signaling in differient colon cancer cells (Umesalma et al., 2015; Yousef et al., 2016a; Yousef et al., 2016b). A number of studies have presented the apoptotic effects of EA or its metabolites (urolithin A and urolithin B) in human colon cancer HT-29, Caco-2, HCT-116 and HCT-15 cells. These effects included: i) the increase ofROS production, ii) the activation of caspase-3, -8, -9 and c-PARP, iii) the promotion of the expression of Bax and cytochrome c, and suppressed Bcl-2 and iv) the augmentation of DNA fragmentation (Cho et al., 2015; Yousef et al., 2016b). Regarding *in vitro* colon cancer model, EA, urolithin A, urolithin B and isourolithin A inhibited cancer cells progression by arresting the cell cycle at G1, S and G2/M phase (Cho et al., 2015; González-Sarrías et al., 2014; González-Sarrías et al., 2017; Yousef et al., 2016b) through the upregulation of p21 (Cho et al., 2015) and downregulation of cyclin D1 expressions (Fig. 4) (Umesalma et al., 2015).

Furthermore, EA synergistically increased the anti-proliferative activity of 5-fluorouracil (5-FU) by activating apoptosis through the decrease of MMP, and increase of Bax/Bcl-2 ratio and caspase-3 activity in HT-29 cells (Kao et al., 2012). Moreover, urolithin A potentiated the chemopreventive effects of both 5-FU and 5'DFUR on Caco-2, HT-29 and SW-480 colon cancer cells by blocking the cell cycle at the G2/M phase by elevating cyclin A and cyclin B1 expressions and inducing apoptosis with increased caspase-8 and -9 activation (González-Sarrías et al., 2015). In resistant HT-29 and SW-620 colon cancer cells, EA derivatives inhibited proliferation by inhibiting the Wnt signaling pathways (Fig. 5) (de Molina et al., 2015). Regarding animal models of CRC, EA prevented the carcinogenesis process by targeting diverse molecular aspects, including i) decrease of TBARS and DNA damage by increasing cellular antioxidant status (Kumar et al., 2012), ii) downregulation of proliferation marker PCNA expression (Umesalma et al., 2014), iii) reduction of the ACF formation by modulating the expression of transcription factor c-MYC-dependent

ornithine decarboxylase (Kumar et al., 2012), iv) decrease of intestinal inflammation by downregulating iNOS and COX-2, and inhibiting NF-κB, STAT3 and p38MAPK pathways (Marín et al., 2013), v) promotion of apoptosis by increasing p53 (Umesalma et al., 2014) expression and finally vi) anti-angiogenesis property and suppressionof MMP-2 and MMP-9 expression in the colon tissue (Umesalma et al., 2014).

4.1.2.3. Rosmarinic acid

The biosynthesis of rosmarinic acid (RA) starts with precursor molecules L-phenylalanine and L-tyrosine, using 4-coumaroyl-CoA as a hydroxycinnamoyl donor and hydroxyphenyllactic acid as a hydroxycinnamoyl acceptor substrate, this reaction is catalyzed by hydroxycinnamoyl transferase (Petersen et al., 2009). Aromatic herbs are the only dietary sources of RA and include basil (*Ocimum basilicum*), marjoram (*Origanum marjoram*), oregano, melissa (*Melissa officinalis*), peppermint (*Mentha* × *piperita*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), spearmint (*Mentha spicata*) and thyme (*Thymus* spp.). A smaller quantity of rosmarinic acid (500 mg/kg dry weight) has been found in the botanically unrelated borage (Borago officinalis) (Crozier et al., 2006).

Rosmarinic acid has been shown to exert anti-cancer effects mainly activating apoptosis through mitochondrial and death receptor-mediated pathways. In COLO-205 cells, RA treatment increased the expression of Fas and FasL, which further activated caspase-8, Bid, Bax and Bad, followed by decreased MMP and increased cytochrome c and AIF expressions in the cytosol (Cheng et al., 2011). Furthermore, elevated cytochrome C activated caspase-9 and -3 pursuing the c-PARP and DNA fragmentation (Cheng et al., 2011).

Regarding *in vivo* studies using carcinogen-treated CRC models, RA exerted chemopreventive effects by decreasing polyp incidence and multiplicity, and ACF formation (Karthikkumar et al., 2012; Venkatachalam et al., 2013), inhibiting abnormal cell proliferation (PCNA) (Karthikkumar et al., 2015) and preventing oxidative damage by reducing TBARS levels and increasing antioxidant enzymes (SOD,

catalase, glutathione reductase, GPx and glutathione) activity (Karthikkumar et al., 2012; Venkatachalam et al., 2013). Furthermore, RA ingestion suppressed the inflammatory mediators including TNF-α, IL-6, COX-2 and NF-κBexpression (Fig. 3) (Karthikkumar et al., 2015), as well as increased apoptosis by elevating the expression of caspase-3, -9, Bax and p53, and suppressed Bcl-2 expression (Venkatachalam et al., 2016) in the colonic tissue.

4.1.2.4. Caffeic acid

Caffeic acid is one of the intermediates in the plant phenylpropanoid pathway starting from the deamination of phenylalanine, which generates cinnamic acid. This is followed by two-step sequential hydroxylation at the 4- and 3-position of the benzyl ring, and cinnamic acid is then converted into caffeic acid via p-coumaric acid. The most abundant hydroxycinnamic acid in food is 5-O-caffeoylquinic acid, the ester of caffeic acid with quinic acid, widely referred to as chlorogenic acid. Coffee is the major dietary source of chlorogenic acids. Apples, red wine, green tea, apricots and prunes contain modest levels of caffeic acid. Herbs are the dietary source of α-hydroxyhydrocaffeic acid, a conjugate of caffeic acid, at concentrations ranging from 10 to 20 g/kg dry basis (Crozier et al., 2006).

Caffeic acid or its derivatives can be considered as a chemopreventive agent in preclinical CRC models both *in vitro* and *in vivo* through the modulation of multiple pathways. In HCT-116, SW-480 and HT-29 cells, caffeic acid phenethyl ester and caffeic acid phenylpropyl ester suppressed cells proliferation by downregulating the expression of p-Akt, mTOR,Erk1/2 and NF-κB, and increasing AMPK (Chiang et al., 2014)and p38MAPK (Tang et al., 2017) signaling cascades. This phytochemical activated apoptosis in a panel of colon cancer cells by generating ROS, decreasing MMP (Jaganathan, 2012) and elevating p53, Bax, caspase-3 (Tang et al., 2017), PARP (Yim et al., 2012) and cytochrome c expression, while Bcl-2 expression was decreased (Tang et al., 2017). Furthermore, it arrested the cell cycle at the G0/G1 phase by suppressing the expression of CDK2, CDK4, cyclin D1, cyclin E,c-MYC and PCNA proteins and elevating the expression of p21cip1/waf1 and p27kip1 proteins in HCT-116, HT-29 and SW-480 colon cancer cells

(Fig. 4) (Chiang et al., 2014; Tang et al., 2017). In a xenograft model of CRC, similar effects were observed with a decrease of tumor growth and increase in survival rate (Chiang et al., 2014; Tang et al., 2017). Furthermore, caffeic acid elevated the EMT marker E-cadherinin with the suppression of N-cadherin, MMP-2 and VEGF expression, inducing anti-invasive and anti-angiogenesis activity (Chiang et al., 2014; Tang et al., 2017).

4.1.3. Resveratrol

Trans-resveratrol, 3,4,′5-trihydroxy-trans-stilbene, is synthesized by condensation of p-coumaroyl CoA with three units of malonyl CoA, each of which donates two carbon atoms in a reaction catalysed by stilbene synthase (STS). Resveratrol occurs as both cis and trans isomers and is present in plant tissues primarily as trans-resveratrol-3-O-glucoside, which is known as piceid and polydatin. A study by Burns et al. determined the levels of trans- and cis-resveratrol in different plants. Grapes (*Vitis vinifera* L.) were found to mainly contain trans-resveratrol glucoside in concentrations ranging from 1.5 to 7.3 μg/g. Aglycone trans-resveratrol was also present in two of the four tested grape samples at a concentration of 0.5 μg/g, while cis-resveratrol was not present in detectable amounts in any of the samples analyzed. The stilbene content of grapes is dictated by three factors: cultivar, disease pressure, and time (Burns et al., 2002).

Resveratrol has been known to generate a comprehensive favourable effect on human health including CRC prevention. A number of studies introducing the anticancer effects of resveratrol in CRC cells or animal models found that it modulated several oncogenic targets, significantly inhibiting colon cancer cell proliferation via suppression of the proliferation marker (Ki-67) and various signaling pathways including NF-κB (Fig. 3) (Buhrmann et al., 2016), Ras, Raf, MEK, Erk1/2(Fig. 2) (Chen et al., 2016), PI3K/Akt (Fig. 6) and Wnt/β-catenin (Fig. 5) (Liu, Y.-Z. et al., 2014), as well as elevating PTEN (Liu, Y.-Z. et al., 2014), PCNA (Yuan et al., 2016), SIRT1 expression (Buhrmann et al., 2016), and modulating focal adhesion molecules (Buhmann et al., 2017). Additionally, resveratrol disrupted β-catenin/TCF complex formation, which decreased Wnt target genes such as cyclin D1, T brachyuryand conductin (Chen et al., 2012).

Interestingly, resveratrol increased the expression of bone morphogenetic protein 9, activating p38 MAPK for inducing anti-proliferative effects in LoVo colon cancer cells (Yuan et al., 2016). In rodent models of CRC, resveratrol reduced tumor growth (Yuan et al., 2016), incidence, and mortality rate by inhibiting the expression of Kras, Braf, Erk, PI3K/Akt and β-catenin pathways in the colon tissue (Liu, Y.-Z. et al., 2014; Saud et al., 2014).

Resveratrol induces anti-inflammatory effects via the inhibition of endotoxin-induced NF-κB activation in human colon cancer Caco-2 and SW-480 cells (Fig. 3) (Panaro et al., 2012). It has been observed that in LPS-treated colon cancer cells resveratrol treatment suppressed both protein and mRNA expression of iNOS and decreased the production of nitric oxide, as well as inhibited the expression of TLR4 and the phosphorylation and degradation of theIκB complex (Panaro et al., 2012). Additionally, this phytochemical also suppressed the expression of PGE2 and COX-2 and reduced the levels of PGE2 receptors, EP1, EP3, and EP4 both in *in vitro* and *in vivo* colon cancer models (Feng et al., 2016). Furthermore, Vam3, a resveratrol dimer, was effective in attenuating the chemically induced colitis associated tumor in rat models, by suppressing the expression of active NF-κBp65 and inflammatory cytokines (IL-6, TNF-α and mouse mast cell protease-1), as well as decreasing infiltration of mast cells and CD11bC Gr1C cells, which exhibit a key role in inducing chronic inflammation (Xuan et al., 2016).

Resveratrol induced apoptosis by activating mitochondria-mediated and non-mediated pathway by upregulating the expression of the pro-apoptotic proteins Bok, Bak1, Bik, Bad, Noxa, Bax, Apaf1 and p53, and at the same time downregulating the expression of anti-apoptotic proteins Bcl-xL, Bcl-2 and Bag1in SW-620 and LoVo cells (Chen et al., 2016; Yuan et al., 2016), as well as increasing the cleaved form of PARP, caspase-3, -7 and -9 in SW-620, Caco-2 and HCT-116 cells (Chen et al., 2016; Liu, B. et al., 2014). Another analogue of resveratrol, bakuchiol, induced TRAIL-associated apoptosis by increasing TRAIL receptors, DR4 and DR5, and caspase-3, -8, -9 and PARP expression via targeting ROS/JNK signaling pathway in HCT-116 (TRAIL sensitive) and HT-29 (TRAIL resistant) colon cancer cells (Park et al., 2016). Furthermore, in HCT-116 cells, HS-1793, a synthetic analogue of resveratrol, induced apoptosis on colon

cancer cells by altering of Bax/Bcl-2 ratio, increasing cytochrome c, caspase-3 and c-PARP expression, and suppressing PI3K/Akt signaling, which induced apoptosis (Kim et al., 2017). Furthermore, resveratrol or its analouge arrested cell cycle at G1 (Liu, B. et al., 2014; Polycarpou et al., 2013), S (Aires et al., 2013; Yuan et al., 2016) and G2/M (Kim et al., 2017) phase, suppressing the progression of colon cancer cells. The expression of cyclin-CDK ckeckpoint proteins cyclin D1, CDK2, CDK4 and PCNA was lowered (Liu, B. et al., 2014; Polycarpou et al., 2013), while p21 levels were elevated after treatment with resveratrol (Fig. 4) (Aires et al., 2013; Liu, B. et al., 2014).

The metabolites of resveratrol suppressed metastatic colon cancer SW-480 cell progression by increasing phosphorylated-histone H2AX expression, and increasing p53 levels (Aires et al., 2013). Additionally, Bax, c-PARP and caspase-3 expression evaluation confirmed the apoptosis induction mediated by resveratrol metabolites (Aires et al., 2013). Pterostilbene is a resveratrol derivative and its metabolite pinostilbene significantly altered the major signaling pathways related to cell propagation, cell cycle and apoptosis by increasing the expression of p53, Bax, c-caspase-3 and c-PARP, and p21cip1/waf1, as well as decreasing the expression levels of cyclin E and p-Rb in HT-29 and HCT-116 colon cancer cells (Sun et al., 2016). 3′-hydroxypterostilbene (HPSB), a natural analogue of pterostilbene, induced chemopreventive effect both in *in vitro* and *in vivo* CRC models (Cheng et al., 2014). In CRC cells, it significantly suppressed cell growth through the downregulation of p-mTOR/p70S6K, PI3K/Akt, p-JNK-1/2, p-Erk-1/2 and p-38MAPK signaling pathways, induced apoptosis by increasing c-PARP and DFF-45, caspase-3, -8 and -9 expression, and activated autophagy via the increase of LC3B I/II proteins (Cheng et al., 2014). In a xenograft mice model, HPSB suppressed tumor growth through the down-regulation of the expression of MMP-9, VEGF, cyclin D1 and COX-2, as well as by the activation of apoptosis in colon tumors (Cheng et al., 2014).

The *in vitro* anti-invasive and anti-metastasis activity of resveratrol was associated with inhibition of MMP-7 (Ji et al., 2013), MMP-9 and C-X-C chemokine receptor type 4 (CXCR4) (Buhrmann et al., 2016) in colon cancer cells.

Several studies addressed the synergistic effect of resveratrol with the combination of natural precursor, etoposide or chemopreventive drug on human colon cancer cell lines (De Maria et al., 2013; Kumazaki et al., 2013; Reddivari et al., 2016). The synergistic effect was accompanied by inhibiting the growth of Caco-2 and DLD-1 cells through downregulating MAPK, Erk-1/2, PI3K/Akt and STAT3 signaling pathways and increasing apoptosis by p53 activation and c-PARP expressions (De Maria et al., 2013; Kumazaki et al., 2013). Another combination of resveratrol and grape seed extract induced chemopreventive activity by eliminating colon CSC in *in vitro* and *in vivo* models of colon carcinogenesis. This combined treatment suppressed Wnt/β-catenin signaling (Fig. 5), cyclin D1 and c-MYC and increased mitochondrial-mediated apoptosis by elevating p53, cytochrome c, Bax/Bcl-2 ratio and c-PARP (Reddivari et al., 2016).

4.1.4. Curcumin

Curcumin derives from the rizome of turmeric, *Curcuma longa* L., a member of the ginger family, Zingiberaceae. PAL catalyses the first step in this pathway, the conversion of l-phenylalanine to cinnamic acid, which in a reaction catalysed by C4H is converted to p-coumaric acid. This is metabolized via a series of hydroxylation and methylation reactions, which leads to ferulic acid. Cinnamin acid, p-coumaric acid and ferulic acid are three different precursors of curcuminoids. Curcuminoid synthase (CUS) is the enzyme responsible for the final steps in the synthesis pathway of curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Katsuyama et al., 2009).

Curcumin can modulate several growth factors and signaling pathways that are accountable for initiation, proliferation and progression of colon cancer. In a panel of colon cancer cells curcumin or its analogue inhibited cellular proliferation or survival rate by targeting various signaling pathways, including the suppression of the expression of EGFR (Qiu et al., 2013), PI3k/Akt/mTOR (Fig. 6) (Jiang et al., 2014; Sato et al., 2017; Wang, J. et al., 2016; Zhu, J. et al., 2013) and its downstream targets EIF2, eIF4/p70S6K (Wang, J. et al., 2016), MEK (Fig. 2) (Fenton and McCaskey, 2013), Wnt/β-catenin (Fig. 5) (Zhang, Z. et al., 2016), GSK-3β kinase (He et al., 2016; Jiang et al., 2014; Montgomery et al., 2016; Murthy et al., 2013;

Sankpal et al., 2016; Sufi et al., 2017; Waghela et al., 2015) and NF-κB (in the presence of TNF-α) (Fig. 3) (Waghela et al., 2015), as well as the increase in the expression of p-Erk1/2 and p-AMPK (Sato et al., 2017) signaling. Additionally, curcumin treatment induced mitochondrial dysfunction, and lysosomal and autophagy activation for inducing cell death, which are usually accompanied by an enhancement in ROS generation, for the development of autophagosome and autosomal degradation, and in lysosomal protein Lamp1 and heat shock protein 70 (HSP70) expressions (Wang, J. et al., 2016). Interestingly, curcumin and several curcumin analogs induced chemopreventive activity in HCT-116 cells by activating nuclear receptors, such as the retinoic acid receptor, vitamin D receptor and retinoid X receptor, inducing similar benefits like vitamin D and A (Batie et al., 2013).

In colon cancer DLD-1, SW620, LoVo, HCT-116 and HT-29 cells, six different types of curcumin analogues suppressed EGFR expression and tyrosine phosphorylation and demonstrated pro-apoptotic effects through the modulation of different molecular targets: increased cytosolic p53, released cytochrome c, activated caspase-3,-7,-9, c-PARP, increased ratio of Bax/Bcl-2 and ROS generation, and finally decreased MMP (Basile et al., 2013; He et al., 2016; Jiang et al., 2014; Montgomery et al., 2016; Murthy et al., 2013; Qiu et al., 2013; Sankpal et al., 2016; Sufi et al., 2017; Waghela et al., 2015; Zhang et al., 2017). Furthermore, curcumin analogue significantly reduced the levels of HSP70 and HSP90, with the former by directly inhibiting apoptosis whereas with the latter by stabilizing various growth factor receptors, including EGFR (Qiu et al., 2013). Over-expression of GRP78 has been related to the increased therapeutic efficacy of curcumin on HT-29 and DLD-1 colon cancer cells by altering apoptosis-related signaling molecules (Bcl2, Bax and Bad) (Chang et al., 2015). Furthermore, curcumin induced Prp4-mediated apoptosis in HCT-15 colon cancer cells by ROS generation and by inhibiting Prp4 expression (Shehzad et al., 2013).

Synthetic derivatives of curcumin induced ER stress-mediated apoptosis in CT-26 cancer cells by activating PERK, eIF2α, ATF4, and GADD153/CHOP expression (Zhang et al., 2017). The effects were also confirmed in a xenograft model of colon cancer, where an inhibition of tumor growth was evidenced

(Zhang et al., 2017). Moreover, autophagic cell death was observed in SW-620 colon cancer cells after curcumin treatment, by activating lysosomal pathway through the upregulation of TFEB, Lamp1, Atp6v1a, Uvrag and Atg9b, and LC3 expression, as well as inhibition of p62, Akt and mTOR signaling pathway (Zhang, J. et al., 2016). Curcumin derivatives also induced ER stress-mediated autophagy in p53 positive HCT-116 colon cancer cells by increasing activation of CHOP, DR5, ATF6, XBP1, GRP78 and HERPUD1 (Basile et al., 2013). The autophagic feature was confirmed by the increased formation of autophagosome and LC3-I to LC3-II conversation in a Beclin-1 independent manner (Basile et al., 2013).

Curcumin and its analogue treatment arrested the cell cycle at G0/G1and G2/M (He et al., 2016; Jiang et al., 2014; Montgomery et al., 2016; Murthy et al., 2013; Sankpal et al., 2016; Sufi et al., 2017; Waghela et al., 2015; Zhang et al., 2017) phase in colon cancer SW480, SW620, CT-26, HCT-116 and HT-29 cells by targeting signaling checkpoint proteins (Fig. 4), such as p21waf-1/cip-1 (Qiu et al., 2013), cyclinD1 (He et al., 2016; Jiang et al., 2014; Montgomery et al., 2016; Murthy et al., 2013; Qiu et al., 2013; Sankpal et al., 2016; Sufi et al., 2017; Waghela et al., 2015), cyclin B1, cdc2 (Zhang et al., 2017), cyclin E1 and Rb (Qiu et al., 2013).

In LoVo and SW-480 colon cancer cells the anti-invasive efficacy of curcumin was associated also with the activation of AMPK and the consequent inhibition of p65-NF-κB, uPA and MMP-9 (Tong et al., 2016). Moreover, it inhibited EMT by increasing NKD2, E-cadherin and axin expressions, and decreasing β-catenin, vimentin and CXCR4 (Zhang, Z. et al., 2016), and adhesion molecules such as Zeb 1, Hef 1 and Claudin 1 expression (Esmatabadi et al., 2015). Analogue of curcumin exhibited anti-angiogenesis activity by decreasing NF-κB expression, which led to a reduction in the expression of HIF-1α, VEGF, p-STAT-3 and COX-2 in HCT-116 and HT-29 colon cancer cells (Rajitha et al., 2017). In agreement with the *in vitro* study, similar effects were observed in a mouse model of colon cancer (Rajitha et al., 2017).

Curcumin or its analogue, combined with other natural compounds or with chemopreventive drugs, stimulated apoptosis, through the activation of caspase cascade, c-PARP, Bax/Bcl-2 ratio, ROS and ROS mediated JNK activation, as well as the reduction of MMP and the transcription factors Sp1, survivin and

NF-κB expression, highlighting an enhanced therapeutic effects (He et al., 2016; Jiang et al., 2014; Montgomery et al., 2016; Murthy et al., 2013; Sankpal et al., 2016; Sufi et al., 2017; Waghela et al., 2015) in a panel of colon cancer cells. Co-delivery of curcumin with TRAIL increased the TRAIL-induced apoptosis effects by increasing DR4 and DR5 both in *in vitro* and *in vivo* models (Yang et al., 2017). Interestingly, in an artificially created tumor microenvironment, curcumin treatment synergistically increased the treatment efficacy of 5-FU by decreasing the crosstalk between CSC and fibroblasts through the suppression of the expression of NF-κB and TGF-β/p-Smad-2 (Buhrmann et al., 2014). Moreover, combined therapy of curcumin analogue and 5-FU induced more pronounced effects compared to drug or compound alone in colon cancer SW-480 and SW-620 cell lines. This combination induced apoptosis by elevating ROS generation and increasing Bax/Bcl-2 and cytochrome c expression, arresting cell cycle at G0/G1 phase, and enhancing ER stress via the upregulation of CHOP and Noxa expression (Zhao, H. et al., 2017). In chemoresistant colon cancer cells, curcumin increased the therapeutic efficiency of conventional drugs by inhibiting the proliferative targets cyclin D1, NF-κB, IκBα, PI3K and Src which are activated after drug treatment (Shakibaei et al., 2015; Shakibaei et al., 2013). Additionally, this combination also activated apoptosis through the increase of pro-apoptotic proteins caspase-3, -8, -9, Bax and PARP expression, as well as decreasing expression of anti-apoptotic Bcl-xL (Shakibaei et al., 2015; Shakibaei et al., 2013). In erlotinib resistant colon cancer cells, curcumin modified the drug resistance signaling pathway by suppressing the expression of α, β integrin and increase in the expression of the PDK4 gene (Javadi et al., 2017). Furthermore, curcumin potentiated the anti-invasive and anti-metastasis activity of 5-FU in HCT-116 cells by suppressing the expression of the CXCR4 and MMP-9 gene (Shakibaei et al., 2015).

In an experimentally induced mouse model of CRC, the anti-neoplastic effect of curcumin was enhanced when it was administered together with diclofenac (Rana et al., 2015a, 2015b). Both agents inhibited PI3-K/Akt/PTEN pathway (Fig. 6) by activating a mitochondrial dependent apoptotic mechanism that is connected with increased expression of pro-apoptotic proteins (Bad and Bax), caspases-3, -9 levels, and concomitant decrease in anti-apoptotic protein (Bcl-2) levels (Rana et al., 2015a). Furthermore, diclofenac

and curcumin overcame the carcinogenic effects of DMH by downregulating telomerase activity, arresting cell progression by diminishing the expression of CDK4, CDK2, cyclin D1 and cyclin E, and consequently activating p53, Rb and p21 expression (Fig. 4) (Rana et al., 2015b). Curcumin significantly attenuated the severity of DSS-induced colitis by suppressing cyclin D1 and CDK4 expression and inhibiting STAT3 signaling (Fig. 7) in mouse colon (Yang et al., 2013). Furthermore, curcumin enhanced the treatment efficacy of high protein diet by suppressing the inflammatory markers (iNOS, COX-2, TNF-α and NO) and reducing colonic proliferation and toxic metabolites (Byun et al., 2015) in the colon and plasma. Oral ingestion of curcumin suppressed the development of pre-neoplastic lesions in the mouse colon by decreasing the expression of TNF-α, COX-2, IL-6, and NF-κB (Fig. 3), as well as increasing AMPK expression (Kubota et al., 2012; Murakami et al., 2013). Furthermore, in obese rat CRC model, combination of curcumin with salsalate decreased pro-inflammatory markers (IL-1β and IL-6), and Akt and NF-κB signaling more significantly compared to curcumin alone (Wu et al., 2017). Curcumin also improved the adipocytokine imbalance by decreasing leptin levels and fatweights (Kubota et al., 2012). Moreover, curcumin reduced oxidative and nitrosative stress, and arginase activity, by inducing apoptosis and suppressing iNOS, increasing TGF-β1 and HES-1expressions as well as reducing ACF formation in the mouse colon (Bounaama et al., 2012).

4.2. Terpenoids

Terpenoids are derived from the universal C5 precursor isopentenyl diphosphate (IPP) and their allylicisomer dimethylallyl diphosphates (DMAPP), which in higher plants are generated through two independent pathways located in separate intracellular compartments. In cytosol, IPP is derived from the long-known mevalonic acid pathway, which starts with the condensation of acetyl-CoA, while in plastids IPP is formed from pyruvate and glyceraldehydes 3-phosphate. In the second phase of terpene biosynthesis, IPP and DMAPP are used by prenyltransferases in head-to-tail condensation reactions to produce geranylgeranyl diphosphate (GGDP), generanyl diphosphate (GDP) and farnesyl diphosphate

(FDP), precursors of monoterpenes, sesquiterpenes and diterpenes. In the third stage of terpene biosynthesis, the allylicprenyldiphosphates of GDP, FDP and GGDP are used by terpene syntetase to form monoterpenes, sesquiterpenes, and diterpenes, respectively (Cheng et al., 2007).

4.2.1. Ursolic acid

Ursolic Acid (UA), a natural pentacyclic triterpenoid carboxylic acid, is effective in inhibiting the growth of CRC in *in vitro* and *in vivo* models by suppressing multiple biomarkers of inflammation, proliferation, invasion, angiogenesis and metastasis. For example, UA treatment significantly suppressed the phosphorylation of STAT3 (Fig. 7), Akt/mTOR (Fig. 6), Erk1/2, JNK, p38MAPK (Fig. 2) and p70S6K, as well as the key mediators of sonic hedgehog signaling in both *in vitro* and *in vivo* in colon cancer models (Lin et al., 2013a; Lin et al., 2013b; Wang, J. et al., 2013b). UA enhanced apoptotic cell death in genetically modified colon cancer cells by increasing ROS generation and modulating multiple apoptotic markers through the increase of Bax, cleavage of caspase-3, -9 and PARP, the release of cytochrome c, and the reduction of Bcl-2, Bcl-xL, cFLIP, cyclin D1 and survivin expression (Koh et al., 2012; Lin et al., 2013b; Prasad et al., 2012; Wang, J. et al., 2013b). Moreover, it suppressed cell growth by arresting the cell cycle at G1/S phase by suppressing cyclin D1 and CDK4 expression as well as increasing p21 expression (Fig. 4) (Lin et al., 2013b).

UA exerted anti-inflammatory effects by inhibiting constitutive activation of COX-2, PGE2 and NF-κB (Prasad et al., 2012; Wang, J. et al., 2013b). Additionally, UA and its derivatives inhibited APC-mutated colon cancer cells growth by promoting the N-terminal phosphorylation and consequent proteasomal degradation of β-catenin and its dependent gene cyclin D1, c-MYC and AXIN 2 (Fig. 5) (Kim, J.-H. et al., 2014).

Anti-invasive and anti-angiogenesis activity was also found in colon cancer cells after UA treatment, through the downregulation of the expression of MMP-2, VEGF, ICAM-1 and bFGF, and upregulation of CDH1 expression (Prasad et al., 2012; Shan et al., 2016; Wang, J. et al., 2013a; Wang, J. et al., 2013b).

These effects were also confirmed in a xenograft model of CRC (Lin et al., 2013a). Furthermore, in chemoresistant colon cancer RKO, LoVo, and SW-480 cells, UA suppressed MDR1 expression by reducing HIF-1α accumulation and downregulated VEGF expression (Shan et al., 2016). A more prominent effect was observed when UA was combined with capecitabine (Prasad et al., 2012) or melatonin (Wang, J. et al., 2013a) in LoVo, HCT-116 and SW-480 colon cancer cells. In a mouse model of CRC, UA ingestion significantly repressed ascites formation, tumor volume and distant organ metastasis by suppressing microvessel density (CD31) and biomarkers of proliferation (Ki-67), and subsequently inhibiting the expression of EGFR, STAT3, NF-κB, and β-catenin (Prasad et al., 2012).

4.2.2. Betulinic acid

On HT-29 and HCT-116 colon cancer cells, the anticancer activity of betulinic acid, a naturally occurring pentacyclic triterpenoid, and its analogue are associated with an increase in apoptosis through i) the increase of ROS generation and DNA fragmentation and ii) the reduction of MMP activity, increase of caspase-3,-9, Bax and Bad, as well as decrease of Bcl-xl and Bcl-2 expressions (Chakraborty et al., 2015). Similarly, betulinic acid analogue induced autophagic death of HT-29 cells by altering the expression of Atg 5, Atg7, Atg5-Atg 12, LC3B, Beclin-1 and p62 proteins. In addition, this analogue treatment induced autophagolysosome formation with colocalization of LAMP-1 with LC3B, and p62 with lysosomes and decreased the proteasomal degradation pathway (Dutta et al., 2016).

4.3. Organosulfur Compounds

Organosulfur compounds include glucosinolates (GSL) derived from the glucosinolate–myrosinase (substrate–enzyme) system found in cruciferous crops such as cabbages, broccoli (*Brassica oleracea* L.) and watercress (*Nasturtium officinale* R. Br.), and those derived from the alliin-alliinase system found within Allium crops, such as garlic (*Alluim sativum* L.), onions (*Alluim cepa* L.) and leeks (*Alluim porrum* L.). The myrosinase-glucosinolate system catalyzing hydrolysis of GSL initially involves cleavage of the

thioglucoside linkage, yielding D-glucose and an unstable thiohydroximate-O-sulphonate which spontaneously rearranges, resulting in the production of a sulphate and one of a wide range of possible reaction products. In Allium species, sulphur-containing compounds are formed by the hydrolysis of non-volatile alkyl and alkenyl-substituted l-cysteine sulphoxides due to the action of the enzyme alliinase following tissue disruption. Of these precursors, 2-propenyl-l-cysteine sulphoxide (alliin) is characteristic of leeks and garlic, and 1-propenyl-l-cysteine sulphoxide (isoalliin) is characteristic of onions. Methyl and propyl-l-cysteine sulphoxides also occur in these and other Allium species (Crozier et al., 2006). According to epidemiologic studies, an opposite link was observed between the ingestion of organosulfur compounds and the frequency of various types of cancer (Moriarty et al., 2007).

4.3.1. Sulforaphane

Sulforaphane is an isothiocyanate that induces chemopreventive activity in *in vitro*and *in vivo* CRC models by modulating multiple molecular mechanisms. For example, it induced apoptotic death of colon cancer HCT-116 and Caco-2 cells by i) increasing ROS production and Ca^{2+} levels, and decreasing MMP, ii) activating cytochrome c, DR4, DR5, TRAIL and caspase-3, -8,-9, -4 and PARP cleavage, iii) upregulating pro-apoptotic proteins (Bid and Bax) and downregulating anti-apoptotic proteins (XIAP, Bcl-2 and Mcl-1) (Lan et al., 2017; Liu et al., 2016; Wang, M. et al., 2012), iv) activating MEK2, JNK, Erk1/2 and p38 signaling pathways (Fig. 2) (Byun et al., 2016; Lan et al., 2017) and v) increasing ER stress associated protein (Calpain 1, ATF6α, ATF6β, GADD153, and GRP78) expressions (Liu et al., 2016; Wang, M. et al., 2012). Several studies also reported that the anti-proliferative effects of sulforaphane are associated with the arrest of cell cycle at G1 and G2/M (Byun et al., 2016; Liu et al., 2016; Wang, M. et al., 2012) phase, by upregulating p27kip1 (Chung et al., 2015), cyclin A, cyclin B, CDK2, and WEE1 (Liu et al., 2016; Wang, M. et al., 2012) as well as downregulating SKP2 (Chung et al., 2015), cdc25C and CDK1 (Liu et al., 2016; Wang, M. et al., 2012) protein expressions (Fig. 4).

Additionally, sulforaphane inhibited microtubule polymerization and elicited ROS generation via glutathione depletion in HCT-116 cells (Byun et al., 2016), while in HT-29 and Caco-2 cells it regulated Nrf2 activity by inducing phase II enzyme, uridinediphosphate-glucuronosyltransferase 1A (UGT1A) expression, which plays a vital role in detoxifying procarcinogenesis or in the carcinogenesis process (Wang, M. et al., 2012). Moreover, rapamycin increased the chemopreventive effects of sulforaphane by activating autophagy by inducing LC3-II, and increasing UGT1A through continuous activation of Nrf2 and hPXR signaling pathways (Wang, M. et al., 2013; Wang et al., 2014). The novel thiourea-functionalized silicon nanoparticles (SiNPs) have been effectively synthesized using sulforaphane and allylamine and investigated for their anticancer effects specifically utilizing the EGFR inhibitory activity. The results suggested that this novel nanosystem degraded overexpressed EGFRin colon cancer Caco-2 cells (Behray et al., 2016). Under hypoxic conditions, sulforaphane inhibited colon cancer HCT-116 cell angiogenesis and migration by inhibiting HIF-1α and VEGF expression (Kim et al., 2015). Moreover, in a xenograft mouse model of CRC, supplementation of sulforaphane significantly reduced tumor volume and increased CDK1, MK2, and p38 phosphorylation in colon tissue (Byun et al., 2016).

4.3.2. Indole-3-carbinol

Only a limited number of studies have addressed the anti-cancer effects of indole-3-carbinol (hydrolysis form glucobrassicin) in colon cancer cells. Indole-3-carbinol or its derivatives induced cytotoxic effects in HT-29 and HCT-116 colon cancer cells by inhibiting Akt and its downstream targets such as mTOR (Fig. 6) and GSK-3β (Fig. 5) and induced apoptosis by activating the pro-apoptotic proteins p53 and p21, and decreasing the anti-apoptotic protein Bcl-2 and Akt-mediated phosphorylation of ASK1 (Ser83) (Kim et al., 2011). Additionally, the oral consumption of this potent Akt inhibitor inhibited cancer cell growth in *in vivo* xenograft animal model (Kim et al., 2011). In poorly differentiated colonic cancer Colo-320 and HCT-116 cells, indole-3-carbinol derivatives elevated N-MYC downstream regulated gene-1 (NDRG1) expression, inducing apoptotic cell death (Lerner et al., 2011). In colon cancer SW-480 and HCT-116 cells,

another derivative of indole-3-carbinol inhibited the cell cycle progression through reducing the levels of cyclin D1 and A, and inhibited TNF-α induced NF-κB activation (Fig. 3) (Fadlalla et al., 2015).

5. Metabolic engineering of dietary phytochemicals

5.1. Metabolic engineering strategy for flavonoid production in plants

Over the past decade, increasing knowledge of flavonoid biosynthesis and the important function these compounds serve in plants, animals and human nutrition have made the biosynthetic pathways to flavonoids and isoflavonoids excellent targets for metabolic engineering. Recent strategies have introduced novel structural or regulatory genes, and the antisense or sense suppression of genes in these pathways (Crozier et al., 2006). For example, tomatoes (*Solanum lycopersicum* L.) naturally only produce low amounts of kaempferol and quercetin in the fruit peel, and the introduction and over expression of the regulatory genes Lc and C1 from maize led to an increase in kaempferol formation of up to 60%, mainly in fresh fruits. Moreover, introducing the CHI gene from Petunias resulted in an increase of up to 70% in quercetin formation in peel. Expressing Lc and C1 in potatoes (*Solanum tuberosum* L.) also led to a marked accumulation of kaempferol in the tubers (Forkmann and Martens, 2001). Isoflavones are primarily limited to legumes, with the first step in biosynthesis being catalysed by isoflavone synthase (IFS). Recent cloning of the gene encoding IFS has opened the way for engineering isoflavone formation in crop plants that normally lack these compounds. Introducing the soybean IFS gene driven by the 35S promotor in non-legume plants resulted in the conversion of naringenin to the isoflavone genistein, a phytoestrogen of high medical interest.

The greatest enrichment in anthocyanins has been engineered in purple tomatoes by combining the expression of an R2R3MYB protein (Rosea 1) and a bHLH protein (Delila) from snapdragons (*Antirrhinum majus*) (Butelli et al., 2008). The success in engineering tomatoes was the expression of regulatory genes under the control of their specific promoter (from the E8 gene of tomatoes) that is activated once fruit has reached complete development and flavor synthesis has been completed. The cultures yield substantially

more (~20 mg/g dry weight) anthocyanins than conventional cultures (~1–2 mg/g dry weight) (Zhang et al., 2014).

Bogs et al. have shown that overexpression of VvMYBPA1 or VvMYBPA2 in grapevine hairy roots induces an approximately 5-fold increase in accumulation of condensed tannins (CT). The CT composition of VvMYBPA1 and VvMYBPA2 over expressing hairy roots is very similar, with a significant increase in EGC and almost no change in the degree of polymerization and level of CT galloylation (Bogs et al., 2007).

5.2. Metabolic engineering strategy for phenols.

Carbon flux into the phenylpropanoid pathway is regulated by PAL, one of the most thoroughly studied plant enzymes. PAL transformes L-phenylalanine (L-Phe) to trans-cinnamic acid (t-CA) and ammonia.

Bauer et al. studied the impact of PAL activity on phenolic production in transgenic roots of *Coleus blumei* benth harbouring the *Arabidopsis thaliana* PAL1 gene, under the control of the CaMV 35S promoter, along with empty vector and wild-type roots. Transgenic roots with high PAL activity (between 67 and 350 %) had lower growth rates, lower amounts of total phenolics, RA and chlorogenic acid, but increased concentrations of caffeic acid compared to wild-type (Bauer et al., 2011).

Muir et al. integrated mutant *Escherichia coli* (*E. coli*) aroE, devoid of functional SDH, with the plant gene from *A. thaliana* and *Juglans regia* L., so as to produce GA. In addition, transgenic *Nicotiana tabacum* lines expressing *Juglans regia* SDH produced a 500% increase in GA accumulation (Muir et al., 2011).

5.3. Metabolic engineering of resveratrol

Many authors have explored overexpression of Vsts genes as a valuable strategy for increasing trans-resveratrol concentrations. For example, the inclusion of the Vitis Vsts gene in various plants was found to increase trans-resveratrol levels. In fact, the highest trans-resveratrol levels (around 350 mg/g-1 dry weight)

were obtained after transforming the genome of 41B rootstock with a chimeric gene combining alfalfa PR10 promoter and Vsts1 (Coutos-Thévenot et al., 2001).

Another metabolic engineering approach employed in the production of resveratrol uses microorganisms as cell factories for high production of phytochemicals. Studies by Watts et al. (2006) introduced and expressed gene coding for 4-coumaroyl Coa ligase from *A. thaliana*, and STS from *Arachis hypogaea*, L. in *E. coli*. The production of resveratrol in this recombinant strain is > 100 mg/l when phenylpropionic acid precursor is added to the medium. The same strategy has also been exploited in *S. cerevisiae* with results comparable to those obtained in *E. coli* (Beekwilder et al., 2006).

Finally, resveratrol can be obtained from commercial feedstocks with an overall yield of about 71 % (Farina et al., 2006).

5.4. Production of curcuminoids by *Escherichia coli* (*E. coli*)

The efficient production of curcuminoid in *E. coli* has been attributed to the use of CUS - a type III polyketide synthase - and exogenous supplementation with corresponding precursors. Katsuyama et al. (2008) efficiently produced curcuminoids in recombinant *E. coli* constructed with an artificial biosynthetic pathway comprising PAL (from *Rhodotorula rubra*), C4H (from *Lithospernum erythrorhizon* Siebold & Zucc) and CUS (from *Oryza sativa* L.) in tyrosine and/or phenylalanine medium, with yields from 20 to 100 mg/1. Improved yields between 90 and 110 mg/l were achieved upon removal of PAL in a different system, which increased p-coumaroyl-CoA concentration using phenylpropanoid acids (p-coumaric acid, cinnamic acid and ferulic acid) as supplementing agents (Katsuyama et al., 2008).

5.5. Metabolic engineering of terpenoids

The first studies aimed at altering the monoterpene profile of plants focused on mint (Mentha spp.) and petunias (*Petunia atkinsiana* D. Don ex W.H. Baxter). The aim was in overexpressing the gene from spearmint (*Mentha spicata* L.) encoding limonene synthase (MsLS) in peppermint (*Mentha piperita* L.)

stable integration of the gene was successfully induced, but the terpene profile of the plants was not clearly altered. Arabidopsis was found to be an extremely useful model plant in metabolic engineering strategies aimed at increasing terpenoid production. To evaluate the potential of Arabidopsis in producing monoterpenoid and sesquiterpenoids, Aharoni et al. (2003) used the strawberry (*Fragaria x ananassa (Duchesne ex Weston) Duchesne ex Rozier*) FaNES1 gene (coding for nerolidol synthase 1). Linalool and nerolidol were not detected in wild type plants, whereas transgenic plants contained up to 1.5 µg/g (fresh weight).

5.6. Metabolic engineering of aliphatic glucosinolates

As far as organosulfur compounds are concerned, metabolic engineering in plants can be achieved through various approaches targeting the biosynthetic pathway, the regulatory genes of GSL biosynthetic pathway, and the modulation of transcription factors. For example, Zang et al. (2008) produced transgenic Chinese cabbage by over expressing the Arabidopsis MAM1, CYP79F1, and CYP83A1 gene. They obtained increased levels of aliphatic glucosinolate, gluconapin, and glucobrassicanapin in the MAM1 line, whereas in the CYP83A1 line, gluconapin and glucobrassicanapin levels increased 4,5- and 2-fold respectively. More recently, Mikkelsen et al. (2010) engineered the glucoraphanin and Indole glucosinolate pathways into the non-cruciferous tobacco plant. Their results showed that while the successful production of glucoraphanin was achieved, the corresponding chain elongated Leu- and Ileu-derived GSLs were 5–8-fold higher than those of obtained glucoraphanin levels, due to the greater availability of Leu/Ileu than Met in tobacco for GSL biosynthesis GSL.

6. Roles of epigenetic modifications induced by dietary phytochemicals for colorectal cancer prevention: preclinical studies

Epigenetic modifications are imperative in regulating DNA methylation, histone modifications, and miRNA-mediated alterations. Consequently, irregular epigenetic alteration may lead to the initiation and

continuation of various cancers (Dawson and Kouzarides, 2012). For this reason, inverse epigenetic alteration is an excellent target for the chemopreventive and therapeutic intention (Gulei et al., 2017; Schnekenburger et al., 2014). Several phytochemicals can reverse epigenetic changes for preventing colon cancer (Fig. 8 and Table 2).

Anthocyanin protected colon cancer HT-29 cells from DNA damage which may occur during topoisomerase poisonsaction (Esselen et al., 2011). Additionally, anthocyanin demethylated tumor suppressor genes in *in vitro* colon cancer models (HCT-116, Caco-2 and SW-480 cells) via suppressing DNA (cytosine-5)-methyltransferase (DNMT)1 and DNMT3B, and decreasing the expression of Wnt and its downstream targets β-catenin and c-MYC (Wang, L.-S. et al., 2013).

Epigenetic modification caused by genistein treatment suppressed colon cancer cells growth through i) inhibiting human DNA topoisomerase II activity (Mizushina et al., 2013), ii) increasing dickkopf-1 (DKK1) expression via induction of histone acetylation at the DKK1 promoter region (Wang, H. et al., 2012), and iii) reducing the histone deacetylase 1 (HDAC1) protein level through suppression of HDAC activity (Groh et al., 2013).

EGCG modulated the retinoid X receptor α (RXRα) promoter methylation in CpG island methylator phenotype positive cell lines, where RXRα expression was decreased. Subsequently, this led to a decrease in nuclear β-catenin and cyclin D1 expressions, andarrest of cell proliferation (Morris et al., 2016). Furthermore, EGCG induced therapeutic effects in methylation-sensitive colon cancer cells by decreasing the expression of DNMT3A and HDAC3 by degrading these proteins (Moseley et al., 2013). The combination treatment of EGCG and sodium butyrate induced epigenetic modification in colon cancer RKO, HCT-116 and HT-29 cells by increasing the levels of double strand breaks as evaluated by gamma-H2A histone family member X (γ-H2AX) protein levels, and generation of histone H3 hyperacetylation (Saldanha et al., 2014). Furthermore, reduced DNMT1levels and CpG methylation as well as increased HDAC1 levels were observed after the combination treatments (Saldanha et al., 2014). An EGCG derivative, AcEGCG, promoted epigenetic alterations of several genes that were supposed to play an vital

role in inflammation-induced colon cancer in mouse model. Pretreatment withAcEGCG significantly decreased acetylation of histone 3 lysine 9 (H3K9) and p65/RelA expression which led to the suppression of transcriptional activity of NF-κB (Chiou et al., 2012).

Silibinin induced epigenetic modification on *in vitro* CRC model through inhibiting DNMT properties and exerted synergistic activity with HDAC inhibitors which led to cancer cell death (Kauntz et al., 2013). Furthermore, kaempferol has a special epigenetic action by increasing hyperacetylation of histone complex H3 in colon cancer HCT-116 cells (Berger et al., 2013).

In different genetic background of Caco-2 (K-Ras+/ p53-) and HCT-116 (K-Ras-/p53+) colon cancer cells, EA inhibited cells proliferation by suppressing p-Akt (Thr308) expression in KRAS siRNA transfected cells (Yousef et al., 2016a). Additionally, physiologically relevant mixtures of colonic metabolites of urolithins induced anticancer potential in HT-29, Caco-2 and SW-480 colon cancer cells by modulating miRNA levels, such as upregulation of p21cip1 encoding CDKN1A, together with downregulation of miR-224 and upregulation of miR-215 levels (González-Sarrías et al., 2016). Caffeic acid suppressed the HCT-116 cell proliferation by decreasing the DNA topoisomerase II activity which blocked the cell cycle progression at the G2/M phase (Kuriyama et al., 2013).

In an APC^{CKO}/K-ras^{mut} mouse model of CRC, resveratrol treatment decreased tumor growth through elevating miR-96 production, which suppressed Kras expression in colon tissue (Saud et al., 2014). In addition, resveratrol increased the chemopreventive activity of 5-FU in resistant colon cancer DLD-1 cells by increasing the expression of miR-34a as well as suppressing the expression E2F3 and its downstream target Sirt1, which contributed to apoptosis induction (Kumazaki et al., 2013). Furthermore, in HT-29 colon cancer cells, resveratrol suppressed the survival rate by activating NADPH oxidase, induced DNA damage by elevating the histone gH2AX levels and at the same time induced defense mechanism by increasing Sirt6 levels (San Hipólito-Luengo et al., 2017). The combination treatment of resveratrol and quercetin suppressed the expression of specificity protein (Sp) transcription factors Sp1, Sp3, and Sp4, together with Sp-dependent anti-apoptotic survivin gene levels in HT-29 cells (Del Follo-Martinez et al., 2013).

Moreover, this combination reduced miR-27a and stimulated zinc finger protein ZBTB10, which acts as a Sp-repressor and plays an important role for downregulation of the Sp factors (Del Follo-Martinez et al., 2013).

Curcumin suppressed colon cancer HCT-116 cell proliferation by increasing miR-491, which further suppressed PEG10 and Wnt/β-catenin signaling pathway (Li et al., 2018). Furthermore, it suppressed HT-29 cells growth anchorage-independently and reduced CpG methylation in DLEC1 promoter, resulting in a decrease of histone deacetylases subtypes (HDAC4, 5, 6, and 8) and DNA methyltransferases expression (Guo et al., 2015). Moreover, curcumin induced ROS generation and suppressed the SP transcription factor by downregulating miR-20a, miR-27a and miR-17-5p (Gandhy et al., 2012). A similar effect was also observed in multidrug resistance colon cancer SW-480 cells (Noratto et al., 2013). In a genetically modified HCT-116 $p53^{-/-}$ and HCT-116 $p53^{+/+}$colon cancer cells, the combination of curcumin with ascorbic acid induced alteration in a large number of genes such as proliferation-related genes (RHOD), signal transduction genes (EGFR, WWC1, CHRNB4, DTX2, CRIM1, VPS41), apoptosis-regulated genes (DFFB), transporter genes (ABCA1), mRNA metabolism genes (NR2F2, HNRNPR, RBBP4, TGM2, SRSF4, andPDK1) and DNA repair genes (TOPBP1, RPA2), inducing chemoprevention (Ooko et al., 2017). Interestingly, diflourinated-curcumin (CDF) caused a marked reduction in miR-21 expression in chemo-resistant colon cancer HCT-116 and HT-29 cells by restoring PTEN levels with subsequent decrease in Akt phosphorylation (Roy et al., 2013). Downregulated miR-21 induced differentiation of chemoresistant colon cancer cells (HT-29 and HCT-116) and increased the therapeutic efficiency of conventional and non-conventional drugs (Yu et al., 2013). Furthermore, CDF significantly increased the expression of both miR-34a and miR-34c in cells by decreasing the expression of the downstream target Notch-1, thus acting as a demethylating compound (Roy et al., 2012). Curcumin analogue increased the transcription factor recognized as the aryl hydrocarbon receptor activity, compared to native curcumin, inducing more cancer cells death by activating apoptosis in a panel of colon cancer cells (Megna et al., 2017).

BA inhibited colon cancer SW-480 and RKO cell growth by inducing proteasome-dependent and independent suppression of the Sp transcription factors Sp1, Sp3 and Sp4, and Sp-regulated genes, including cyclin D1, survivin, VEGF, EGFR, p65-NFκB and pituitary tumor transforming gene-1 (Chintharlapalli et al., 2011). Downregulation of the Sp transcription factors was mediated by elevating ROS generation and ROS induced repression of miR-27a, and production of the Sp repressor gene ZBTB10 (Chintharlapalli et al., 2011). Furthermore, in a xenograft model of CRC, BA treatment reduced tumor volume and growth as well as markedly suppressed the expression of Sp1, Sp3 and Sp4 (Chintharlapalli et al., 2011).

Sulforaphane induced chemopreventive activity by regulating epigenetic modification in HCT-116 and RKO colon cancer cells. The effects were accomplished by downregulating oncogenic miR-21 by suppressing HDAC1, which further inhibited hTERT mRNA, telomerase protein and enzymatic levels (Martin et al., 2018). Moreover, in HT-29 and HCT-116 colon cancer cells, sulforaphane induced Nrf2 activity by regulating functional pseudogene, NMRAL2P, and Nrf2-dependent NQO1 induction by acting as a co-activator (Johnson et al., 2017). Indole-3-carbinol or its derivatives induced cytotoxic effects in multiple CRC cells (DLD1, HCT-116, HT-29, LS513, and RKO) by activating the aryl hydrocarbon receptor through CYP1A1 mRNA expression and inducing apoptosis (Megna et al., 2016).

7. Promising therapies with phytochemicals on colon cancer: clinical studies

A case control study in Korean and Vietnamese population evaluated the relationship between isoflavone and CRC. It was observed that the higher quartile of total isoflavone, daidzein and genistein consumption had an inverse relationship with CRC, particularly in women and there was no heterogeneity in CRC risk in relation to isoflavone concentrations in plasma between the two different populations (Ko et al., 2017). Moreover, a large prospective cohort study and the Netherlands cohort study did not find any association between flavonoid intake and CRC risk (Nimptsch et al., 2015; Simons et al., 2009). Even though clinical studies are still few, a positive relationship between consumption of dietary phytochemicals and lower risk

of CRC has been noted (Table 3) and there are some registered clinical trials in a number of concerned areas (Table 4).

Compared to preclinical studies, only a small number of clinical trials has addressed the effect of curcumin for CRC prevention. The preventive mechanism was accompanied by i) decreasing ACF number by improving the delivered system of curcumin (Carroll et al., 2011), ii) increasing the p53 and Bax expression, reducing Bcl-2 expression and inducing apoptosis of tumor cells (He et al., 2011), iii) decreasing the inflammation marker PGE2 production in the blood (Sharma et al., 2004), iv) decreasing DNA oxidation in malignant tissue (Garcea et al., 2005) and v) improving cancer patients' immunity by increasing T helper 1 cells (Xu et al., 2017). A combined therapy of curcumin and quercetin decreased the number and size of adenomatous polyps in FAP patients without any side effects (Cruz–Correa et al., 2006). Moreover, curcumin followed by silibinin decreased colon polyp formation in the case of multiple colorectal adenomas patients without any mutations of APC and MYH gene (Alfonso-Moreno et al., 2017). The confirmation that supports the defensive effect of curcumin against CRC in humans is still very incomplete when compared with that acquired in preclinical studies.

To our knowledge only three clinical studies have reported the effect of resveratrol on human CRC patients. Ingestion of resveratrol decreased the proliferation marker Ki-67 by 5% in the tissue of malignant and normal mucosa (Patel et al., 2010). Cleaved caspase-3 significantly increased in the hepatic tissue after intake of resveratrol in hepatic metastasis CRC patients compared to placebo (Howells et al., 2011). No difference was observed in the other biomarkers of the serum and in the hepatic tissue between the same groups (Howells et al., 2011). However, low dosages of grape powder or resveratrol intake did not inhibit the expression of Wnt pathway in tissue from CRC patients but decreased the Wnt target gene expression in normal colonic mucosa (Nguyen et al., 2009). Until now, inadequate conformity exists between the anticancer activities of resveratrol found in *in vitro* and *in vivo* studies and those presented in clinical studies.

Few clinical studies have examined the effect of EGCG or green tea extract on CRC patients and some of them are ongoing in clinical trials. Ingestion of green tea extract for one year reduced the incidence of metachronous colorectral adenomas, as well as the size of relapsed adenomas in high risk CRC patients (Shimizu et al., 2008). Similarly, in a randomized trial, positive association was observed between diet supplementation with green tea extract and metachronous colorectal adenoma in Korean patients. In this study, daily consumption of green tea extract once a day for one year significantly reduced the number of recurrent polyps and relapsed adenomas, and decreased occurrences of metachronous adenoma compared to the control group (Shin et al., 2017). Additionally, long term consumption of EGCG with apigenin decreased the rate of colon neoplasia in CRC patients with resected colon cancer (Hoensch et al., 2008). Moreover, daily intake of green tea polyphenols (containing EGCG) significantly decreased the hepatic arterial infusion-induced oxidative stress in CRC patients with liver metastasis (Baba et al., 2012).

Consumption of bilberry anthocyanin extract decreased the quantified proliferation marker (Ki-67) by 7% in CRC patients, while the concentration of IGF-1 was not reduced significantly in plasma (Thomasset et al., 2009). Furthermore, silibinin increased the clinical effectiveness of regorafenib in the treatment of metastatic colorectal patients. Combined treatment of silybin with regorafenib increased the survival rate of patients with additional defense effects on drug-induced liver damage (Belli et al., 2017). In CRC patients, a significant amount of EA derivatives and urolithins were examined in plasma, urine and colon tissue after ingestion of pomegranate (Nuñez-Sánchez et al., 2014). Significant diversity was observed in the expression of MYC, CTNNB1, CDKN1A, CD44, TYMs and EGFR gene in malignant and normal tissue after intake of EA and urolithins in a tissue- and gene-specific manner but the effects in colon tissue were not related with the specific metabotypes and the level of EA and urolithins (Nuñez-Sánchez et al., 2017). Moreover, Nuñez-Sánchez et al. did not find any association among miRNA and urolithins in colon tissue of the CRC patients (Nuñez-Sánchez et al., 2015). Increasing consumption of non-tea compounds, mainly quercetin, was inversely associated with CRC risk (Kyle et al., 2010). Dietary supplementation of

flavonoids decreased the oxidative stress in lymphocytes of patients with colon cancer caused by food mutagens (Kurzawa-Zegota et al., 2012).

8. Conclusions and prospects

Plant foods are rich in phytochemicals exerting protective activities useful in CRC prevention. To date, major advances have been made on the identification of several affected molecular pathways, which are involved in the progression of CRC. The potentiality of most dietary phytochemicals has been examined only in preclinical trials, either *in vitro* or *in vivo*. However, a limited number of ongoing or completed clinical trials for several dietary phytochemicals, including curcumin, resveratrol, quercetin, anthocyamin, genistein, EGCG, ellagic acid and ellagitannins (Table 3 and Table 4) have been performed in diverse pathological conditions, which supports the possible use of these dietary phytochemicals in the prevention or treatment of CRC. The growing interest in these natural compounds has led to many studies being performed with the aim of improving the production of these phytochemicals in genetically modified plants. These investigations have led to the identification of plant foods enriched in protective substances. However, the low bioavailability of dietary phytochemicals is a major issue of concern to researchers. Many studies on the other hand which address in depth phytochemical derivatives, synthetic analogs or nanoparticles would be a solution for these limitations (Santos et al., 2013; Xie et al., 2016), as the efficacy of curcumin (Alizadeh et al., 2012; Jiang et al., 2014), resveratrol (Chen et al., 2016), EGCG (Xiao et al., 2015), sulforaphane (Behray et al., 2016), betulinic acid (Dutta et al., 2016), etc. have been reported to be increased compared to the "parent" compound administration.

In addition, the microbial composition in the intestine is an emerging aspect in CRC vulnerability, because of the various patho-physiological influences of microorganisms which are connected with cancer development; likewise, probiotics have been taken under consideration in the reduction of carcinogenesis through diverse mechanisms. Nonetheless, further investigations in rodent models as well as vigorous epidemiologic and interventional human studies are essential. Future research on the epigenetic regulation

by diet in the gut will show the way to the advancement of safer, preventive or therapeutic agents to counteract CRC.

It is important that the efficiency of dietary phytochemicals in CRC prevention be deeply understood. Future research should target on i) precise categorization of dietary phytochemicals, ii) alteration of phase II metabolism and gut microbiota and their effect on metabolism, bioavailability, and toxicity of other drugs, iii) a much deeper understanding of the molecular targets and their relevant mechanisms, iv) determination of the impact on *in vivo* studies, v) examination of safety doses and efficiency on prospective human studies, and vi) consideration of numerous pharmacokinetic challenges such as bioavailability, drug-drug interactions, and metabolic instability.

Conflict of interest

The authors declare no conflicts of interest.

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Abbreviation

ACF, aberrant crypt foci; AIF, apoptosis inducing factor; AMPK, AMP-activated protein kinase; ANS, anthocyanidin Synthase; AOM, azoxymethane; AP-1, activator protein-1; APC, adenomatous polyposis coli; ATF, activating transcription factor; ATG, autophagy-related protein; Bad, Bcl-2-associated death; Bak, Bcl-2 homologous antagonist/killer; Bax, B-cell lymphoma 2 associated X protein; Bcl-2, B-cell lymphoma; Bid, BH3-interacting domain death agonist; Bik, Bcl-2 interacting killer; Braf, B rapidly accelerated fibrosarcoma; cdc, cell division cycle; CDK, cyclin-dependent kinase; C4H, cinnamate 4-hydroxylase; CHI, chalcone isomerase; CHOP, CCAAT-enhancer-binding protein homologous protein;

CHS, chalcone synthase; CIN, chromosomal instability; CIMP, CpG island methylator phenotype; CIAP-2, cellular inhibitor of apoptosisprotein-1;COX-2, cyclooxygenase 2; CRC, colorectal cancer; CSC, cancer stem cell;CT, condensed tannins; CUS, curcuminoid synthase; CXCR4, C-X-C chemokine receptor type 4; DAHP, 3-deoxy-D-arabino-heptulosonate 7-phosphate synthase; DKK1, dickkopf-related protein 1;DMAPP, dimethylallyl diphosphates; DMH, 1,2-dimethylhydrazine; DNMT, DNA methyltransferase; DR, death receptor; DSS, 4,4-dimethyl-4-silapentane-1-sulfonic acid; EA, ellagic acid; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; eIF2α, eukaryotic initiation factor 2 alpha; EMT, epithelial–mesenchymal transition; ER, endoplasmic reticulum; Erk 1/2, extracellular-signal-regulated kinase 1/2; FAP, familial adenomatous polyposis; FDP, farnesyl diphosphate; F3'H, flavanone 3-Hydroxylase; FLS, flavonol synthase; 5-FU, 5-fluorouracil; GA, gallic acid; GADD45α, growth arrest and DNA damage-45 alpha; GDP, generanyl diphosphate; GGDP, geranylgeranyl diphosphate; GRP-78, glucose-regulated protein-78; GPx, glutathione peroxidase; GSK-3β, glycogen synthase kinase 3-β; GSL, glucosinolates; HDAC1, histone deacetylase 1; HIF-1, hypoxia-inducible factor 1; HSP-70, heat shock protein 70; IFS, isoflavone synthase; IGF-1, insulin-like growth factor 1; IL, interleukin; iNOS, inducible nitric oxide synthase; IPP, isopentenyl diphosphate; IRE-1, inositol requiring kinase-1; JNK, Jun N-terminal kinase; Kras, Kirsten rat sarcoma virus oncogene homolog; MAPK, mitogen-activated protein kinase; MCI-1, mild cognitive impairment; MMP-2, matrix metalloproteinase 2; MMP, mitochondrial membrane potential; MSI, microsatellite instability; mTORC1, mammalian target of rapamycin complex 1; c-MYC, Myc proto-oncogen; NF-κB, nuclear factor kappa B; Nrf2, nuclear related factor 2; PAL, phenylalanine ammonia-lyase; PARP, poly (ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PERK, protein kinase-like ER kinase; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PP2Ac, protein phosphatase 2 catalytic subunit alpha; RA, rosmarinic acid; Rb, retinoblastoma; ROS, reactive oxygen species; RXRα, retinoid X receptor alpha; SDH, shikimate dehydrogenase; SIRT1, sirtuin 1; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; STS, stilbene

synthase; TBARS, thiobarbituric acid reactive substances; TGF-β, transforming growth factor beta; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha, TRAIL, TNF-related apoptosis-inducing ligand; UGT1A, uridine diphosphate-glucuronosyltransferase 1A; VEGR, vascular endothelial growth factor; Wnt, wingless-type; XBP1, X-box-binding protein one; XIAP, X-linked inhibitor of apoptosis protein.

References

Abreu, M.T., Peek, R.M., 2014. Gastrointestinal malignancy and the microbiome. Gastroenterology 146(6), 1534-1546. e1533.

Afrin, S., Giampieri, F., Gasparrini, M., Forbes-Hernandez, T.Y., Varela-López, A., Quiles, J.L., Mezzetti, B., Battino, M., 2016. Chemopreventive and therapeutic effects of edible berries: A focus on colon cancer prevention and treatment. Molecules 21(2), 169.

Aggarwal, B.B., Gupta, S.C., Kim, J.H., 2011. Historical perspectives on tumor necrosis factor and its superfamily: twenty-five years later, a golden journey. Blood 119, 651-665.

Aggarwal, B.B., Ichikawa, H., 2005. Molecular targets and anticancer potential of indole-3-carbinol and its derivatives. Cell cycle 4(9), 1201-1215.

Aharoni, A., Giri, A.P., Deuerlein, S., Griepink, F., de Kogel, W.J., Verstappen, F.W.A., Verhoeven, H.A., Jongsma, M.A., Schwab, W., Bouwmeester, H.J., 2003. Terpenoid metabolism in wild-type and transgenic Arabidopsis plants. Plant Cell 15(12), 2866-2884.

Ahmed, F.E., 2004. Effect of diet, life style, and other environmental/chemopreventive factors on colorectal cancer development, and assessment of the risks. J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev. 22(2), 91-148.

Aires, V., Limagne, E., Cotte, A.K., Latruffe, N., Ghiringhelli, F.O., Delmas, D., 2013. Resveratrol metabolites inhibit human metastatic colon cancer cells progression and synergize with chemotherapeutic drugs to induce cell death. Mol. Nutr. Food Res. 57(7), 1170-1181.

Alfonso-Moreno, V., López-Serrano, A., Moreno-Osset, E., 2017. Chemoprevention of polyp recurrence with curcumin followed by silibinin in a case of multiple colorectal adenomas. Rev. Esp. Enferm. Dig. 109(12), 875.

Alizadeh, A.M., Khaniki, M., Azizian, S., Mohaghgheghi, M.A., Sadeghizadeh, M., Najafi, F., 2012. Chemoprevention of azoxymethane-initiated colon cancer in rat by using a novel polymeric nanocarrier–curcumin. Eur. J. Pharmacol. 689(1-3), 226-232.

Alumkal, J.J., Slottke, R., Schwartzman, J., Cherala, G., Munar, M., Graff, J.N., Beer, T.M., Ryan, C.W., Koop, D.R., Gibbs, A., 2015. A phase II study of sulforaphane-rich broccoli sprout extracts in men with recurrent prostate cancer. Invest. New Drugs 33(2), 480-489.

Amado, N.G., Predes, D., Fonseca, B.F., Cerqueira, D.M., Reis, A.H., Dudenhoeffer, A.C., Borges, H.L., Mendes, F.A., Abreu, J.G., 2014. Isoquercitrin suppresses colon cancer cell growth in vitro by targeting the Wnt/β-catenin signaling pathway. J. Biol. Chem. 289(51), 35456-35467.

Ashihara, H., Deng, W.W., Mullen, W., Crozier, A., 2010. Distribution and biosynthesis of flavan-3-ols in Camellia sinensis seedlings and expression of genes encoding biosynthetic enzymes. Phytochemistry 71(5-6), 559-566.

Atanasov, A.G., Waltenberger, B., Pferschy-Wenzig, E.M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E.H., 2015. Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol. Adv. 33(8), 1582-1614.

Aura, A.-M., 2008. Microbial metabolism of dietary phenolic compounds in the colon. Phytochem. Rev. 7(3), 407-429.

Baba, S., Osakabe, N., Natsume, M., Yasuda, A., Muto, Y., Hiyoshi, T., Takano, H., Yoshikawa, T., Terao, J., 2005. Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of Perilla frutescens extract in humans. Eur. J. Nutr. 44(1), 1-9.

Baba, Y., Sonoda, J.I., Hayashi, S., Tosuji, N., Sonoda, S., Makisumi, K., Nakajo, M., 2012. Reduction of oxidative stress in liver cancer patients by oral green tea polyphenol tablets during hepatic arterial infusion chemotherapy. Exp. Ther. Med. 4(3), 452-458.

Basile, V., Belluti, S., Ferrari, E., Gozzoli, C., Ganassi, S., Quaglino, D., Saladini, M., Imbriano, C., 2013. bis-Dehydroxy-Curcumin triggers mitochondrial-associated cell death in human colon cancer cells through ER-stress induced autophagy. PLoS One 8(1), e53664.

Batie, S., Lee, J.H., Jama, R.A., Browder, D.O., Montano, L.A., Huynh, C.C., Marcus, L.M., Tsosie, D.G., Mohammed, Z., Trang, V., 2013. Synthesis and biological evaluation of halogenated curcumin analogs as potential nuclear receptor selective agonists. Bioorganic Med. Chem. 21(3), 693-702.

Bauer, N., Fulgosi, H., Jelaska, S., 2011. Overexpression of phenylalanine ammonia-lyase in transgenic roots of Coleus blumei alters growth and rosmarinic acid synthesis. Food Technol. Biotechnol. 49(1), 24-31.

Beekwilder, J., Wolswinkel, R., Jonker, H., Hall, R., de Vos, C.H.R., Bovy, A., 2006. Production of resveratrol in recombinant microorganisms. Appl. Environ. Microbiol. 72(8), 5670-5672.

Behray, M., Webster, C.A., Pereira, S., Ghosh, P., Krishnamurthy, S., Al-Jamal, W.T., Chao, Y., 2016. Synthesis of diagnostic silicon nanoparticles for targeted delivery of thiourea to epidermal growth factor receptor-expressing cancer cells. ACS Appl. Mater. Interfaces 8(14), 8908-8917.

Belli, V., Sforza, V., Cardone, C., Martinelli, E., Barra, G., Matrone, N., Napolitano, S., Morgillo, F., Tuccillo, C., Federico, A., 2017. Regorafenib in combination with silybin as a novel potential strategy for the treatment of metastatic colorectal cancer. Oncotarget 8(40), 68305.

Bendardaf, R., Buhmeida, A., Hilska, M., Laato, M., Syrjanen, S., Syrjanen, K., Collan, Y., Pyrhonen, S., 2008. VEGF-1 expression in colorectal cancer is associated with disease localization, stage, and long-term disease-specific survival. Anticancer Res. 28(6B), 3865-3870.

Berger, A., Venturelli, S., Kallnischkies, M., Böcker, A., Busch, C., Weiland, T., Noor, S., Leischner, C., Weiss, T.S., Lauer, U.M., 2013. Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases. J. Nutr. Biochem. 24(6), 977-985.

Bhatia, V., Falzon, M., 2015. Restoration of the anti-proliferative and anti-migratory effects of 1, 25-dihydroxyvitamin D by silibinin in vitamin D-resistant colon cancer cells. Cancer Lett. 362(2), 199-207.

Bohn, T., McDougall, G.J., Alegría, A., Alminger, M., Arrigoni, E., Aura, A.-M., Brito, C., Cilla, A., El, S.N., Karakaya, S., 2015. Mind the gap—deficits in our knowledge of aspects impacting the bioavailability of phytochemicals and their metabolites—a position paper focusing on carotenoids and polyphenols. Mol. Nutr. Food Res. 59(7), 1307-1323.

Bogs, J., Jaffé, F.W., Takos, A.M., Walker, A.R., Robinson, S.P., 2007. The grapevine transcription factor VvMYBPA1 regulates proanthocyanidin synthesis during fruit development. Plant Physiol. 143(3), 1347-1361.

Boland, C.R., Goel, A., 2010. Microsatellite instability in colorectal cancer. Gastroenterology 138(6), 2073-2087. e2073.

Bounaama, A., Djerdjouri, B., Laroche-Clary, A., Le Morvan, V., Robert, J., 2012. Short curcumin treatment modulates oxidative stress, arginase activity, aberrant crypt foci, and TGF-β1 and HES-1 transcripts in 1,2-dimethylhydrazine-colon carcinogenesis in mice. Toxicology 302(2-3), 308-317.

Braicu, C., Mehterov, N., Vladimirov, B., Sarafian, V., Nabavi, S.M., Atanasov, A.G., Berindan-Neagoe, I., 2017. Nutrigenomics in cancer: Revisiting the effects of natural compounds. Semin. Cancer Biol. 46, 84-106.

Buhrmann, C., Kraehe, P., Lueders, C., Shayan, P., Goel, A., Shakibaei, M., 2014. Curcumin suppresses crosstalk between colon cancer stem cells and stromal fibroblasts in the tumor microenvironment: potential role of EMT. PLoS One 9(9), e107514.

Buhrmann, C., Shayan, P., Popper, B., Goel, A., Shakibaei, M., 2016. Sirt1 is required for resveratrol-mediated chemopreventive effects in colorectal cancer cells. Nutrients 8(3), 145.

Buhrman, C., Shayan, P., Goel, A., Shakibaei, M., 2017. Resveratrol regulates colorectal cancer cell invasion by modulation of focal adhesion molecules.Nutrints. 9, 1073.

Bulzomi, P., Galluzzo, P., Bolli, A., Leone, S., Acconcia, F., Marino, M., 2012. The pro-apoptotic effect of quercetin in cancer cell lines requires ERβ-dependent signals. J. Cell. Physiol. 227(5), 1891-1898.

Burns, J., Gardner, P.T., O'Neil, J., Crawford, S., Morecroft, I., McPhail, D.B., Lister, C., Matthews, D., MacLean, M.R., Lean, M.E.J., 2000. Relationship among antioxidant activity, vasodilation capacity, and phenolic content of red wines. J. Agric. Food Chem. 48(2), 220-230.

Burns, J., Yokota, T., Ashihara, H., Lean, M.E.J., Crozier, A., 2002. Plant foods and herbal sources of resveratrol. J. Agric. Food Chem. 50(11), 3337-3340.

Butelli, E., Titta, L., Giorgio, M., Mock, H.P., Matros, A., Peterek, S., Schijlen, E.G.W.M., Hall, R.D., Bovy, A.G., Luo, J., 2008. Enrichment of tomato fruit with health-promoting anthocyanins by expression of select transcription factors. Nat.Biotechnol. 26(11), 1301-1308.

Byun, S.Y., Kim, D.B., Kim, E., 2015. Curcumin ameliorates the tumor-enhancing effects of a high-protein diet in an azoxymethane-induced mouse model of colon carcinogenesis. Nutr. Res. 35(8), 726-735.

Byun, S., Shin, S.H., Park, J., Lim, S., Lee, E., Lee, C., Sung, D., Farrand, L., Lee, S.R., Kim, K.H., 2016. Sulforaphene suppresses growth of colon cancer-derived tumors via induction of glutathione depletion and microtubule depolymerization. Mol. Nutr. Food Res. 60(5), 1068-1078.

Carroll, R.E., Benya, R.V., Turgeon, D.K., Vareed, S., Neuman, M., Rodriguez, L., Kakarala, M., Carpenter, P.M., McLaren, C., Meyskens, F.L., 2011. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev. Res. 4(3), 354-364.

Cătană, C.S., Mehterov, N., Atanasov, A.G., Berindan-Neagoe, I., 2018. Natural products with anti-aging potential: Affected targets and molecular mechanisms. Biotechnol. Adv., https://doi.org/10.1016/j.biotechadv.2018.1003.1012.

Cerezo-Guisado, M.I., Zur, R., Lorenzo, M.J., Risco, A., Martín-Serrano, M.A., Alvarez-Barrientos, A., Cuenda, A., Centeno, F., 2015. Implication of Akt, ERK1/2 and alternative p38MAPK signalling pathways in human colon cancer cell apoptosis induced by green tea EGCG. Food Chem. Toxicol. 84, 125-132.

Chakraborty, B., Dutta, D., Mukherjee, S., Das, S., Maiti, N.C., Das, P., Chowdhury, C., 2015. Synthesis and biological evaluation of a novel betulinic acid derivative as an inducer of apoptosis in human colon carcinoma cells (HT-29). Eur. J. Med. Chem. 102, 93-105.

Chang, Y.J., Huang, C.Y., Hung, C.S., Chen, W.Y., Wei, P.L., 2015. GRP78 mediates the therapeutic efficacy of curcumin on colon cancer. Tumor Biol. 36(2), 633-641.

Charepalli, V., Reddivari, L., Radhakrishnan, S., Vadde, R., Agarwal, R., Vanamala, J.K.P., 2015. Anthocyanin-containing purple-fleshed potatoes suppress colon tumorigenesis via elimination of colon cancer stem cells. J. Nutr. Biochem. 26(12), 1641-1649.

Cheng, A.X., Lou, Y.G., Mao, Y.B., Lu, S., Wang, L.J., Chen, X.Y., 2007. Plant terpenoids: biosynthesis and ecological functions. J. Integr. Plant Biol. 49(2), 179-186.

Chen, H.J., Hsu, L.S., Shia, Y.T., Lin, M.W., Lin, C.M., 2012. The β-catenin/TCF complex as a novel target of resveratrol in the Wnt/β-catenin signaling pathway. Biochem. Pharmacol. 84(9), 1143-1153.

Chen, H., Jin, Z.L., Xu, H., 2016. MEK/ERK signaling pathway in apoptosis of SW620 cell line and inhibition effect of resveratrol. Asian Pac. J. Trop. Med. 9(1), 49-53.

Cheng, A.C., Lee, M.F., Tsai, M.L., Lai, C.S., Lee, J.H., Ho, C.T., Pan, M.H., 2011. Rosmanol potently induces apoptosis through both the mitochondrial apoptotic pathway and death receptor pathway in human colon adenocarcinoma COLO 205 cells. Food Chem. Toxicol. 49(2), 485-493.

Cheng, T.C., Lai, C.S., Chung, M.C., Kalyanam, N., Majeed, M., Ho, C.T., Ho, Y.S., Pan, M.H., 2014. Potent anti-cancer effect of 3′-hydroxypterostilbene in human colon xenograft tumors. PLoS One 9(11), e111814.

Chiang, E.P.I., Tsai, S.Y., Kuo, Y.H., Pai, M.H., Chiu, H.L., Rodriguez, R.L., Tang, F.Y., 2014. Caffeic acid derivatives inhibit the growth of colon cancer: involvement of the PI3-K/Akt and AMPK signaling pathways. PLoS One 9(6), e99631.

Chintharlapalli, S., Papineni, S., Lei, P., Pathi, S., Safe, S., 2011. Betulinic acid inhibits colon cancer cell and tumor growth and induces proteasome-dependent and-independent downregulation of specificity proteins (Sp) transcription factors. BMC Cancer 11(1), 371.

Chiou, Y.S., Ma, N.J.L., Sang, S., Ho, C.-T.,Wang, Y.J., Pan, M.H., 2012. Peracetylated (−)-epigallocatechin-3-gallate (AcEGCG) potently suppresses dextran sulfate sodium-induced colitis and colon tumorigenesis in mice. J. Agric. Food Chem. 60(13), 3441-3451.

Cho, H., Jung, H., Lee, H., Yi, H.C., Kwak, H.k., Hwang, K.T., 2015. Chemopreventive activity of ellagitannins and their derivatives from black raspberry seeds on HT-29 colon cancer cells. Food Funct. 6(5), 1675-1683.

Cho, H.J., Park, J.H.Y., 2013. Kaempferol induces cell cycle arrest in HT-29 human colon cancer cells. J. Cancer Prev. 18(3), 257.

Cho, J.K., Park, J.W., Song, S.C., 2012. Injectable and biodegradable poly (organophosphazene) gel containing silibinin: its physicochemical properties and anticancer activity. J. Pharm. Sci. 101(7), 2382-2391.

Chow, H.H.S., Cai, Y., Hakim, I.A., Crowell, J.A., Shahi, F., Brooks, C.A., Dorr, R.T., Hara, Y., Alberts, D.S., 2003. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. Clin. Cancer Res. 9(9), 3312-3319.

Chung, Y.K., Or, R.C.H., Lu, C.H., Ouyang, W.T., Yang, S.Y., Chang, C.C., 2015. Sulforaphane down-regulates SKP2 to stabilize p27KIP1 for inducing antiproliferation in human colon adenocarcinoma cells. J. Biosci. Bioeng. 119(1), 35-42.

Cincin, Z.B., Unlu, M., Kiran, B., Bireller, E.S., Baran, Y., Cakmakoglu, B., 2015. Apoptotic effects of quercitrin on DLD-1 colon cancer cell line. Pathol. Oncol. Res. 21(2), 333-338.

Coldham, N.G., Darby, C., Hows, M., King, L.J., Zhang, A.Q., Sauer, M.J., 2002. Comparative metabolism of genistin by human and rat gut microflora: detection and identification of the end-products of metabolism. Xenobiotica 32(1), 45-62.

Coutos-Thévenot, P., Poinssot, B., Bonomelli, A., Yean, H., Breda, C., Buffard, D., Esnault, R., Hain, R., Boulay, M., 2001. *In vitro* tolerance to *Botrytis cinerea* of grapevine 41B rootstock in transgenic plants expressing the stilbene synthase Vst1 gene under the control of a pathogen-inducible PR 10 promoter. J. Exp. Bot. 52(358), 901-910.

Crozier, A., Clifford, M.N., Ashihara, H., 2006. Plant Secondary Metabolites Occurrence, Structure and Role in the Human Diet. Blackwell publishing. 1(3) 14-19.

Cruz–Correa, M., Shoskes, D.A., Sanchez, P., Zhao, R., Hylind, L.M., Wexner, S.D., Giardiello, F.M., 2006. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin. Gastroenterol. Hepatol. 4(8), 1035-1038.

Custodio, A., Feliu, J., 2013. Prognostic and predictive biomarkers for epidermal growth factor receptor-targeted therapy in colorectal cancer: beyond KRAS mutations. Crit. Rev. Oncol. Hematol. 85(1), 45-81.

Da Silva, M., Jaggers, G.K., Verstraeten, S.V., Erlejman, A.G., Fraga, C.G., Oteiza, P.I., 2012. Large procyanidins prevent bile-acid-induced oxidant production and membrane-initiated ERK1/2, p38, and Akt activation in Caco-2 cells. Free Radic. Biol. Med. 52(1), 151-159.

Dawson, M.A., Kouzarides, T., 2012. Cancer epigenetics: from mechanism to therapy. Cell 150(1), 12-27.

De Maria, S., Scognamiglio, I., Lombardi, A., Amodio, N., Caraglia, M., Cartenì, M., Ravagnan, G., Stiuso, P., 2013. Polydatin, a natural precursor of resveratrol, induces cell cycle arrest and differentiation of human colorectal Caco-2 cell. J. Transl. Med. 11(1), 264.

de Molina, A.R., Vargas, T., Molina, S., Sánchez, J., Martínez-Romero, J., González-Vallinas, M., González-Vallinas, R., Martín-Hernández, R., de Cedrón, M.G., Dávalos, A., 2015. The ellagic acid derivative 4, 4′-di-O-methylellagic acid efficiently inhibits colon cancer cell growth through a mechanism involving WNT16. J. Pharmacol. Exp. Ther. 353(2), 433-444.

Del Follo-Martinez, A., Banerjee, N., Li, X., Safe, S., Mertens-Talcott, S., 2013. Resveratrol and quercetin in combination have anticancer activity in colon cancer cells and repress oncogenic microRNA-27a. Nutr. Cancer 65(3), 494-504.

Del Rio, D., Rodriguez-Mateos, A., Spencer, J.P.E., Tognolini, M., Borges, G., Crozier, A., 2013. Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid. Redox Signal. 18(14), 1818-1892.

Dethlefsen, L., Eckburg, P.B., Bik, E.M., Relman, D.A., 2006. Assembly of the human intestinal microbiota. Trends Ecol. Evol. 21(9), 517-523.

Dhillon, A.S., Hagan, S., Rath, O., Kolch, W., 2007. MAP kinase signalling pathways in cancer. Oncogene 26(22), 3279.

Dewick, P.M., 2002. Medicinal natural products: a biosynthetic approach. John Wiley & Sons. England, 151–154.

Dixon, R.A., Ferreira, D., 2002. Genistein. Phytochemistry 60(3), 205-211.

Dominguez-Perles, R., Medina, S., Moreno, D.Á., García-Viguera, C., Ferreres, F., Gil-Izquierdo, Á., 2014. A new ultra-rapid UHPLC/MS/MS method for assessing glucoraphanin and sulforaphane bioavailability in human urine. Food Chem. 143, 132-138.

Du, Q., Wang, Y., Liu, C., Wang, H., Fan, H., Li, Y., Wang, J., Zhang, X., Lu, J., Ji, H., 2016. Chemopreventive activity of GEN-27, a genistein derivative, in colitis-associated cancer is mediated by p65-CDX2-β-catenin axis. Oncotarget 7(14), 17870.

Duan, L., Ding, W., Liu, X., Cheng, X., Cai, J., Hua, E., Jiang, H., 2017. Biosynthesis and engineering of kaempferol in *Saccharomyces cerevisiae*. Microb. Cell Fact. 16(1), 165.

DuPont, M.S., Day, A.J., Bennett, R.N., Mellon, F.A., Kroon, P.A., 2004. Absorption of kaempferol from endive, a source of kaempferol-3-glucuronide, in humans. Eur. J. Clin. Nutr. 58(6), 947.

Dutta, D., Chakraborty, B., Sarkar, A., Chowdhury, C., Das, P., 2016. A potent betulinic acid analogue ascertains an antagonistic mechanism between autophagy and proteasomal degradation pathway in HT-29 cells. BMC Cancer 16(1), 23.

Eid, H.M., Wright, M.L., Anil Kumar, N.V., Qawasmeh, A., Hassan, S.T.S., Mocan, A., Nabavi, S.M., Rastrelli, L., Atanasov, A.G., Haddad, P.S., 2017. Significance of microbiota in obesity and metabolic diseases and the modulatory potential by medicinal plant and food ingredients. Front. Pharmacol. 8, 387.

Enayat, S., Ceyhan, M.Ş., Taşkoparan, B., Stefek, M., Banerjee, S., 2016. CHNQ, a novel 2-Chloro-1, 4-naphthoquinone derivative of quercetin, induces oxidative stress and autophagy both *in vitro* and *in vivo*. Arch. Biochem. Biophys. 596, 84-98.

Esmatabadi, M.J.D., Farhangi, B., Safari, Z., Kazerooni, H., Shirzad, H., Zolghadr, F., Sadeghizadeh, M., 2015. Dendrosomal curcumin inhibits metastatic potential of human SW480 colon cancer cells through Down-regulation of Claudin1, Zeb1 and Hef1-1 gene expression. Asian Pac. J. Cancer Prev. 16, 2473-2481.

Espín, J.C., González-Sarrías, A., Tomás-Barberán, F.A., 2017. The gut microbiota: A key factor in the therapeutic effects of (poly) phenols. Biochem. Pharmacol. 139, 82-93.

Esselen, M., Fritz, J., Hutter, M., Teller, N., Baechler, S., Boettler, U., Marczylo, T.H., Gescher, A.J., Marko, D., 2011. Anthocyanin-rich extracts suppress the DNA-damaging effects of topoisomerase poisons in human colon cancer cells. Mol. Nutr. Food Res. 55(S1).

Etxeberria, U., Fernández-Quintela, A., Milagro, F.I., Aguirre, L., Martínez, J.A., Portillo, M.P., 2013. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. J. Agric. Food Chem. 61(40), 9517-9533.

Fadlalla, K., Elgendy, R., Gilbreath, E., Pondugula, S.R., Yehualaeshet, T., Mansour, M., Serbessa, T., Manne, U., Samuel, T., 2015. 3-(2-Bromoethyl)-indole inhibits the growth of cancer cells and NF-κB activation. Oncol. Rep. 34(1), 495-503.

Farina, A., Ferranti, C., Marra C., 2006. An improved synthesis of resveratrol. Nat. Prod. Res. 20(3), 247-252.

Feng, M., Zhong, L.X., Zhan, Z.Y., Huang, Z.H., Xiong, J.P., 2016. Resveratrol treatment inhibits proliferation of and induces apoptosis in human colon cancer cells. Med. Sci. Monit. 22, 1101.

Fenton, J.I., McCaskey, S.J., 2013. Curcumin and docosahexaenoic acid block insulin-induced colon carcinoma cell proliferation. Prostaglandins Leukot. Essent. Fatty Acids 88(3), 219-226.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., Bray, F., 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136(5), E359-E386.

Fielden, M.R., Samy, S.M., Chou, K.C., Zacharewski, T.R., 2003. Effect of human dietary exposure levels of genistein during gestation and lactation on long-term reproductive development and sperm quality in mice. Food Chem. Toxicol. 41(4), 447-454.

Forester, S.C., Choy, Y.Y., Waterhouse, A.L., Oteiza, P.I., 2014. The anthocyanin metabolites gallic acid, 3-O-methylgallic acid, and 2, 4, 6-trihydroxybenzaldehyde decrease human colon cancer cell viability by regulating pro-oncogenic signals. Mol. Carcinog. 53(6), 432-439.

Forkmann, G., Martens, S., 2001. Metabolic engineering and applications of flavonoids. Curr. Opin. Biotechnol. 12(2), 155-160.

Fraga, C.G., Galleano, M., Verstraeten, S.V., Oteiza, P.I., 2010. Basic biochemical mechanisms behind the health benefits of polyphenols. Mol. Aspects Med. 31(6), 435-445.

Fung, T.T., Hu, F.B., Wu, K., Chiuve, S.E., Fuchs, C.S., Giovannucci, E., 2010. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. Am. J. Clin. Nutr. 92(6), 1429-1435.

Gandhy, S.U., Kim, K., Larsen, L., Rosengren, R.J., Safe, S., 2012. Curcumin and synthetic analogs induce reactive oxygen species and decreases specificity protein (Sp) transcription factors by targeting microRNAs. BMC Cancer 12(1), 564.

Gao, Z., Guo, B., Gao, R., Zhu, Q., Qin, H., 2015. Microbiota disbiosis is associated with colorectal cancer. Front Microbiol. 6, 20.

Garcea, G., Berry, D.P., Jones, D.J.L., Singh, R., Dennison, A.R., Farmer, P.B., Sharma, R.A., Steward, W.P., Gescher, A.J., 2005. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol. Biomarkers Prev. 14(1), 120-125.

Goldstein, N.S., Armin, M., 2001. Epidermal growth factor receptor immunohistochemical reactivity in patients with American Joint Committee on cancer stage IV colon adenocarcinoma. Cancer 92(5), 1331-1346.

González-Barrio, R., Edwards, C.A., Crozier, A., 2011. Colonic catabolism of ellagitannins, ellagic acid, and raspberry anthocyanins: in vivo and in vitro studies. Drug Metab. Dispos. 39(9), 1680-1688.

González-Sarrías, A., Giménez-Bastida, J.A., Núñez-Sánchez, M.Á., Larrosa, M., García-Conesa, M.T., Tomás-Barberán, F.A., Espín, J.C., 2014. Phase-II metabolism limits the antiproliferative activity of urolithins in human colon cancer cells. Eur. J. Nutr. 53(3), 853-864.

González-Sarrías, A., Núñez-Sánchez, M.Á., García-Villalba, R., Tomás-Barberán, F.A., Espín, J.C., 2017. Antiproliferative activity of the ellagic acid-derived gut microbiota isourolithin A and comparison with its urolithin A isomer: the role of cell metabolism. Eur. J. Nutr. 56(2), 831-841.

González-Sarrías, A., Tomé-Carneiro, J., Bellesia, A., Tomás-Barberán, F.A., Espín, J.C., 2015. The ellagic acid-derived gut microbiota metabolite, urolithin A, potentiates the anticancer effects of 5-fluorouracil chemotherapy on human colon cancer cells. Food Funct. 6(5), 1460-1469.

González-Sarrías, A., Núñez-Sánchez, M.Á., Tomé-Carneiro, J., Tomás-Barberán, F.A., García-Conesa, M.T., Espín, J.C., 2016. Comprehensive characterization of the effects of ellagic acid and urolithins on colorectal cancer and key-associated molecular hallmarks: MicroRNA cell specific induction of CDKN1A (p21) as a common mechanism involved. Mol. Nutr. Food Res. 60(4), 701-716.

González-Vallinas, M., González-Castejón, M., Rodríguez-Casado, A., Ramírez de Molina, A., 2013. Dietary phytochemicals in cancer prevention and therapy: a complementary approach with promising perspectives. Nutr. Rev. 71(9), 585-599.

Grimberg, A., Cohen, P., 2000. Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis. J. Cell. Physiol. 183(1), 1-9.

Groh, I.A.M., Chen, C., Lüske, C., Cartus, A.T., Esselen, M., 2013. Plant polyphenols and oxidative metabolites of the herbal alkenylbenzene methyleugenol suppress histone deacetylase activity in human colon carcinoma cells. J. Nutr. Metab. 2013.

Gruca, A., Krawczyk, Z., Szeja, W., Grynkiewicz, G., Rusin, A., 2014. Synthetic genistein glycosides inhibiting EGFR phosphorylation enhance the effect of radiation in HCT 116 colon cancer cells. Molecules 19(11), 18558-18573.

Gugler, R., Leschik, M., Dengler, H.J., 1975. Disposition of quercetin in man after single oral and intravenous doses. Eur. J. Clin. Pharmacol. 9(2-3), 229-234.

Gulei, D., Mehterov, N., Nabavi, S.M., Atanasov, A.G., Berindan-Neagoe, I., 2017. Targeting ncRNAs by plant secondary metabolites: The ncRNAs game in the balance towards malignancy inhibition. Biotechnol. Adv.

Guo, Y., Shu, L., Zhang, C., Su, Z.Y., Kong, A.N.T., 2015. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene *DLEC1*. Biochem. Pharmacol. 94(2), 69-78.

Han, J., Kurita, Y., Isoda, H., 2013. Genistein-induced G2/M cell cycle arrest of human intestinal colon cancer Caco-2 cells is associated with Cyclin B1 and Chk2 down-regulation. Cytotechnology 65(6), 973-978.

Han, M., Song, Y., Zhang, X., 2016. Quercetin suppresses the migration and invasion in human colon cancer caco-2 cells through regulating toll-like receptor 4/nuclear factor-kappa B pathway. Pharmacogn. Mag. 12(Suppl 2), S237.

Hashemzaei, M., Delarami Far, A., Yari, A., Heravi, R.E., Tabrizian, K., Taghdisi, S.M., Sadegh, S.E., Tsarouhas, K., Kouretas, D., Tzanakakis, G., 2017. Anticancer and apoptosis-inducing effects of quercetin *in vitro* and *in vivo*. Oncol. Rep. 38(2), 819-828.

He, G., Feng, C., Vinothkumar, R., Chen, W., Dai, X., Chen, X., Ye, Q., Qiu, C., Zhou, H., Wang, Y., 2016. Curcumin analog EF24 induces apoptosis via ROS-dependent mitochondrial dysfunction in human colorectal cancer cells. Cancer Chemother. Pharmacol. 78(6), 1151-1161.

He, T.C., Sparks, A.B., Rago, C., Hermeking, H., Zawel, L., Da Costa, L.T., Morin, P.J., Vogelstein, B., Kinzler, K.W., 1998. Identification of c-MYC as a target of the APC pathway. Science 281(5382), 1509-1512.

He, Z.Y., Shi, C.B., Wen, H., Li, F.L., Wang, B.L., Wang, J., 2011. Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest. 29(3), 208-213.

Hodgson, J.M., Morton, L.W., Puddey, I.B., Beilin, L.J., Croft, K.D., 2000. Gallic acid metabolites are markers of black tea intake in humans. J. Agric. Food Chem. 48(6), 2276-2280.

Hoensch, H., Groh, B., Edler, L., Kirch, W., 2008. Prospective cohort comparison of flavonoid treatment in patients with resected colorectal cancer to prevent recurrence. World J. Gastroenterol. 14(14), 2187-2193.

Hoh, C.S.L., Boocock, D.J., Marczylo, T.H., Brown, V.A., Cai, H., Steward, W.P., Berry, D.P., Gescher, A.J., 2007. Quantitation of silibinin, a putative cancer chemopreventive agent derived from milk thistle (Silybum marianum), in human plasma by high-performance liquid chromatography and identification of possible metabolites. J. Agric. Food Chem. 55(7), 2532-2535.

Howells, L.M., Berry, D.P., Elliott, P.J., Jacobson, E.W., Hoffmann, E., Hegarty, B., Brown, K., Steward, W.P., Gescher, A.J., 2011. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics. Cancer Prev. Res. 4(9), 1419-1425.

Hsu, C.P., Shih, Y.T., Lin, B.R., Chiu, C.F., Lin, C.C., 2012. Inhibitory effect and mechanisms of an anthocyanins-and anthocyanidins-rich extract from purple-shoot tea on colorectal carcinoma cell proliferation. J. Agric. Food Chem. 60(14), 3686-3692.

Huang, S., Yang, N., Liu, Y., Gao, J., Huang, T., Hu, L., Zhao, J., Li, Y., Li, C., Zhang, X., 2012. Grape seed proanthocyanidins inhibit colon cancer-induced angiogenesis through suppressing the expression of VEGF and Ang1. Int. J. Mol. Med. 30(6), 1410-1416.

Huxley, R.R., Ansary-Moghaddam, A., Clifton, P., Czernichow, S., Parr, C.L., Woodward, M., 2009. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int. J. Cancer 125(1), 171-180.

Ireson, C.R., Jones, D.J.L., Orr, S., Coughtrie, M.W.H., Boocock, D.J., Williams, M.L., Farmer, P.B., Steward, W.P., Gescher, A.J., 2002. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol. Biomarkers Prev. 11(1), 105-111.

Jaganathan, S.K., 2012. Growth inhibition by caffeic acid, one of the phenolic constituents of honey, in HCT 15 colon cancer cells. Sci. World J. 2012.

Javadi, S., Rostamizadeh, K., Hejazi, J., Parsa, M., Fathi, M., 2017. Curcumin mediated down-regulation of αVβ3 integrin and up-regulation of pyruvate dehydrogenase kinase 4 (PDK4) in Erlotinib resistant SW480 colon cancer cells. Phytother Res. 32(2), 355-364.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Thun, M.J., 2009. Cancer statistics, 2009. CA Cancer J. Clin. 59(4), 225-249.

Jenkinson, F., Steele, R.J.C., 2010. Colorectal cancer screening–methodology. Surgeon 8(3), 164-171.

Ji, Q., Liu, X., Fu, X., Zhang, L., Sui, H., Zhou, L., Sun, J., Cai, J., Qin, J., Ren, J., 2013. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/β-catenin signal pathway. PLoS One 8(11), e78700.

Jiang, Q.G., Li, T.Y., Liu, D.N., Zhang, H.T., 2014. PI3K/Akt pathway involving into apoptosis and invasion in human colon cancer cells LoVo. Mol. Biol. Rep. 41(5), 3359-3367.

Johnson, G.S., Li, J., Beaver, L.M., Dashwood, W.M., Sun, D., Rajendran, P., Williams, D.E., Ho, E., Dashwood, R.H., 2017. A functional pseudogene, NMRAL2P, is regulated by Nrf2 and serves as a coactivator of NQO1 in sulforaphane-treated colon cancer cells. Mol. Nutr. Food Res. 61(4), 1600769.

Kao, T.Y., Chung, Y.C., Hou, Y.C., Tsai, Y.W., Chen, C.H., Chang, H.P., Chou, J.L., Hsu, C.P., 2012. Effects of ellagic acid on chemosensitivity to 5-fluorouracil in colorectal carcinoma cells. Anticancer Res. 32(10), 4413-4418.

Karim, B.O., Rhee, K.J., Liu, G., Zheng, D., Huso, D.L., 2013. Chemoprevention utility of silibinin and Cdk4 pathway inhibition in Apc−/+ ice. BMC Cancer 13(1), 157.

Karthikkumar, V., Sivagami, G., Vinothkumar, R., Rajkumar, D., Nalini, N., 2012. Modulatory efficacy of rosmarinic acid on premalignant lesions and antioxidant status in 1, 2-dimethylhydrazine induced rat colon carcinogenesis. Environ. Toxicol. Pharmacol. 34(3), 949-958.

Karthikkumar, V., Sivagami, G., Viswanathan, P., Nalini, N., 2015. Rosmarinic acid inhibits DMH-induced cell proliferation in experimental rats. J. Basic Clin. Physiol. Pharmacol. 26(2), 185-200.

Katsuyama, Y., Kita, T., Funa, N., Horinouchi, S., 2009. Curcuminoid biosynthesis by two type III polyketide synthases in the herb *Curcuma longa*. J. Biol. Chem. 284 (17), 11160–11170.

Katsuyama, Y., Matsuzawa, M., Funa, N., Horinouchi, S., 2008. Production of curcuminoids by *Escherichia coli* carrying an artificial biosynthesis pathway. Microbiology 154(9), 2620-2628.

Kauntz, H., Bousserouel, S., Gossé, F., Raul, F., 2012a. The flavonolignan silibinin potentiates TRAIL-induced apoptosis in human colon adenocarcinoma and in derived TRAIL-resistant metastatic cells. Apoptosis 17(8), 797-809.

Kauntz, H., Bousserouel, S., Gosse, F., Marescaux, J., Raul, F., 2012b. Silibinin, a natural flavonoid, modulates the early expression of chemoprevention biomarkers in a preclinical model of colon carcinogenesis. Int. J. Oncol. 41(3), 849-854.

Kauntz, H., Bousserouel, S., Gossé, F., Raul, F., 2013. Epigenetic effects of the natural flavonolignan silibinin on colon adenocarcinoma cells and their derived metastatic cells. Oncol. Lett. 5(4), 1273-1277.

Kee, J.Y., Han, Y.H., Kim, D.S., Mun, J.G., Park, J., Jeong, M.Y., Um, J.Y., Hong, S.H., 2016. Inhibitory effect of quercetin on colorectal lung metastasis through inducing apoptosis, and suppression of metastatic ability. Phytomedicine 23(13), 1680-1690.

Khan, I., Paul, S., Jakhar, R., Bhardwaj, M., Han, J., Kang, S.C., 2016. Novel quercetin derivative TEF induces ER stress and mitochondria-mediated apoptosis in human colon cancer HCT-116 cells. Biomed. Pharmacother. 84, 789-799.

Kim, S.H., Choi, K.C., 2013. Anti-cancer effect and underlying mechanism (s) of kaempferol, a phytoestrogen, on the regulation of apoptosis in diverse cancer cell models. Toxicol Res 29(4), 229-234.

Kim, D.H., Kim, M.J., Sung, B., Suh, H., Jung, J.H., Chung, H.Y., Kim, N.D., 2017. Resveratrol analogue, HS-1793, induces apoptotic cell death and cell cycle arrest through downregulation of AKT in human colon cancer cells. Oncol. Rep. 37(1), 281-288.

Kim, D.H., Sung, B., Kang, Y.J., Hwang, S.Y., Kim, M.J., Yoon, J.H., Im, E., Kim, N.D., 2015. Sulforaphane inhibits hypoxia-induced HIF-1α and VEGF expression and migration of human colon cancer cells. Int. J. Oncol. 47(6), 2226-2232.

Kim, D.J., Reddy, K., Kim, M.O., Li, Y., Nadas, J., Cho, Y.Y., Kim, J.E., Shim, J.H., Song, N.R., Carper, A., 2011. (3-Chloroacetyl)-indole, a novel allosteric AKT inhibitor, suppresses colon cancer growth *in vitro* and *in vivo*. Cancer Prev. Res. 4(11), 1842-1851.

Kim, G.T., Lee, S.H., Kim, J.I., Kim, Y.M., 2014. Quercetin regulates the sestrin 2-AMPK-p38 MAPK signaling pathway and induces apoptosis by increasing the generation of intracellular ROS in a p53-independent manner. Int. J. Mol. Med. 33(4), 863-869.

Kim, G.T., Lee, S.H., Kim, Y.M., 2013. Quercetin regulates sestrin 2-AMPK-mTOR signaling pathway and induces apoptosis via increased intracellular ROS in HCT116 colon cancer cells. Eur. J. Cancer Prev. 18(3), 264.

Kim, H.-S., Wannatung, T., Lee, S., Yang, W.K., Chung, S.H., Lim, J.S., Choe, W., Kang, I., Kim, S.S., Ha, J., 2012. Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer. Apoptosis 17(9), 938-949.

Kim, J.H., Kim, Y.H., Song, G.Y., Kim, D.E., Jeong, Y.J., Liu, K.H., Chung, Y.H., Oh, S., 2014. Ursolic acid and its natural derivative corosolic acid suppress the proliferation of APC-mutated colon cancer cells through promotion of β-catenin degradation. Food Chem. Toxicol. 67, 87-95.

Kim, K.H., Dodsworth, C., Paras, A., Burton, B.K., 2013. High dose genistein aglycone therapy is safe in patients with mucopolysaccharidoses involving the central nervous system. Mol. Genet. Metab. 109(4), 382-385.

Ko, K.P., Yeo, Y., Yoon, J.H., Kim, C.S., Tokudome, S., Koriyama, C., Lim, Y.K., Chang, S.H., Shin, H.R., Kang, D., 2017. Plasma phytoestrogens concentration and risk of colorectal cancer in two different Asian populations. Clin. Nutr.

Koh, S.J., Tak, J.K., Kim, S.T., Nam, W.S., Kim, S.Y., Park, K.M., Park, J.W., 2012. Sensitization of ionizing radiation-induced apoptosis by ursolic acid. Free Radic. Res. 46(3), 339-345.

Kubota, M., Shimizu, M., Sakai, H., Yasuda, Y., Terakura, D., Baba, A., Ohno, T., Tsurumi, H., Tanaka, T., Moriwaki, H., 2012. Preventive effects of curcumin on the development of azoxymethane-induced colonic preneoplastic lesions in male C57BL/KsJ-db/db obese mice. Nutr. Cancer 64(1), 72-79.

Kumar, K.N., Raja, S.B., Vidhya, N., Devaraj, S.N., 2012. Ellagic acid modulates antioxidant status, ornithine decarboxylase expression, and aberrant crypt foci progression in 1, 2-dimethylhydrazine-instigated colon preneoplastic lesions in rats. J. Agric. Food Chem. 60(14), 3665-3672.

Kumar, S., Raina, K., Agarwal, C., Agarwal, R., 2014. Silibinin strongly inhibits the growth kinetics of colon cancer stem cell-enriched spheroids by modulating interleukin 4/6-mediated survival signals. Oncotarget 5(13), 4972.

Kumazaki, M., Noguchi, S., Yasui, Y., Iwasaki, J., Shinohara, H., Yamada, N., Akao, Y., 2013. Anti-cancer effects of naturally occurring compounds through modulation of signal transduction and miRNA expression in human colon cancer cells. J. Nutr. Biochem. 24(11), 1849-1858.

Kuriyama, I., Nakajima, Y., Nishida, H., Konishi, T., Takeuchi, T., Sugawara, F., Yoshida, H., Mizushina, Y., 2013. Inhibitory effects of low molecular weight polyphenolics from Inonotus obliquus on human DNA topoisomerase activity and cancer cell proliferation. Mol. Med. Rep. 8(2), 535-542.

Kurzawa-Zegota, M., Najafzadeh, M., Baumgartner, A., Anderson, D., 2012. The protective effect of the flavonoids on food-mutagen-induced DNA damage in peripheral blood lymphocytes from colon cancer patients. Food Chem. Toxicol. 50(2), 124-129.

Kyle, J.A.M., Sharp, L., Little, J., Duthie, G.G., McNeill, G., 2010. Dietary flavonoid intake and colorectal cancer: a case–control study. Br. J. Nutr. 103(3), 429-436.

Lan, H., Yuan, H., Lin, C., 2017. Sulforaphane induces p53-deficient SW480 cell apoptosis via the ROS-MAPK signaling pathway. Mol. Med. Rep. 16(5), 7796-7804.

Lao, C.D., Ruffin, M.T., Normolle, D., Heath, D.D., Murray, S.I., Bailey, J.M., Boggs, M.E., Crowell, J., Rock, C.L., Brenner, D.E., 2006. Dose escalation of a curcuminoid formulation. BMC Complement. Altern. Med. 6(1), 10.

Lao, V.V., Grady, W.M., 2011. Epigenetics and colorectal cancer. Nat. Rev. Gastroenterol. Hepatol. 8(12), 686.

Larrosa, M., Luceri, C., Vivoli, E., Pagliuca, C., Lodovici, M., Moneti, G., Dolara, P., 2009. Polyphenol metabolites from colonic microbiota exert anti-inflammatory activity on different inflammation models. Mol. Nutr. Food Res. 53(8), 1044-1054.

Lee, H.S., Cho, H.J., Kwon, G.T., Park, J.H.Y., 2014a. Kaempferol downregulates insulin-like growth factor-I receptor and ErbB3 signaling in HT-29 human colon cancer cells. Journal of cancer prevention 19(3), 161.

Lee, H.S., Cho, H.J., Yu, R., Lee, K.W., Chun, H.S., Park, J.H.Y., 2014b. Mechanisms underlying apoptosis-inducing effects of Kaempferol in HT-29 human colon cancer cells. International journal of molecular sciences 15(2), 2722-2737.

Lee, J., Kim, Y.S., Lee, J., Heo, S.C., Lee, K.L., Choi, S.W., Kim, Y., 2016. Walnut phenolic extract and Its bioactive compounds suppress colon cancer cell growth by regulating colon cancer stemness. Nutrients 8(7), 439.

Lee, K.W., Bode, A.M., Dong, Z., 2011. Molecular targets of phytochemicals for cancer prevention. Nature Reviews Cancer 11(3), 211.

Leipold, D., Wünsch, G., Schmidt, M., Bart, H.J., Bley, T., Neuhaus, H.E., Bergmann, H., Richling, E., Muffler, K., Ulber, R., 2010. Biosynthesis of ursolic acid derivatives by microbial metabolism of ursolic acid with Nocardia sp. strains—Proposal of new biosynthetic pathways. Process Biochem. 45(7), 1043-1051.

León, I.E., Cadavid-Vargas, J.F., Tiscornia, I., Porro, V., Castelli, S., Katkar, P., Desideri, A., Bollati-Fogolin, M., Etcheverry, S.B., 2015. Oxidovanadium (IV) complexes with chrysin and silibinin: anticancer activity and mechanisms of action in a human colon adenocarcinoma model. J. Biol. Inorg. Chem. 20(7), 1175-1191.

Lepri, S.R., Zanelatto, L.C., da Silva, P.B.G., Sartori, D., Ribeiro, L.R., Mantovani, M.S., 2014. The effects of genistein and daidzein on cell proliferation kinetics in HT29 colon cancer cells: the expression of CTNNBIP1 (β-catenin), APC (adenomatous polyposis coli) and BIRC5 (survivin). Human Cell 27(2), 78-84.

Lerner, A., Grafi-Cohen, M., Napso, T., Azzam, N., Fares, F., 2011. The indolic diet-derivative, 3, 3′-diindolylmethane, induced apoptosis in human colon cancer cells through upregulation of NDRG1. BioMed Res. Int. 2012.

Li, B., Shi, C., Li, B., Zhao, J.M., Wang, L., 2018. The Effects of Curcumin on HCT-116 Cells Proliferation and Apoptosis via the miR-491/PEG10 Pathway. J. Cell. Biochem. 119(4), 3091-3098.

Li, S.K.H., Martin, A., 2016. Mismatch repair and colon cancer: mechanisms and therapies explored. Trends Mol. Med. 22(4), 274-289.

Lin, C.M., Chen, Y.H., Ma, H.P., Wang, B.W., Chiu, J.H., Chua, S.K., Ong, J.R., Shyu, K.G., 2012. Silibinin inhibits the invasion of IL-6-stimulated colon cancer cells via selective JNK/AP-1/MMP-2 modulation *in vitro*. J. Agric. Food Chem. 60(51), 12451-12457.

Lin, J., Chen, Y., Wei, L., Hong, Z., Sferra, T.J., Peng, J., 2013a. Ursolic acid inhibits colorectal cancer angiogenesis through suppression of multiple signaling pathways. Int. J. Oncol. 43(5), 1666-1674.

Lin, J., Chen, Y., Wei, L., Shen, A., Sferra, T.J., Hong, Z., Peng, J., 2013b. Ursolic acid promotes colorectal cancer cell apoptosis and inhibits cell proliferation via modulation of multiple signaling pathways. int. J. Oncol. 43(4), 1235-1243.

Lippert, E., Ruemmele, P., Obermeier, F., Goelder, S., Kunst, C., Rogler, G., Dunger, N., Messmann, H., Hartmann, A., Endlicher, E., 2017. Anthocyanins Prevent Colorectal Cancer Development in a Mouse Model. Digestion 95(4), 275-280.

Liu, B., Zhou, Z., Zhou, W., Liu, J., Zhang, Q., Xia, J., Liu, J., Chen, N., Li, M., Zhu, R., 2014. Resveratrol inhibits proliferation in human colorectal carcinoma cells by inducing G1/S-phase cell cycle arrest and apoptosis through caspase/cyclin-CDK pathways. Mol. Med. Rep. 10(4), 1697-1702.

Liu, K.C., Shih, T.Y., Kuo, C.L., Ma, Y.S., Yang, J.L., Wu, P.P., Huang, Y.P., Lai, K.C., Chung, J.G., 2016. Sulforaphane induces cell death through G2/M phase arrest and triggers apoptosis in HCT 116 human colon cancer cells. Am. J. Chin. Med. 44(06), 1289-1310.

Liu, M., Tian, H.l., Wu, J.H., Cang, R.R., Wang, R.X., Qi, X.H., Xu, Q., Chen, X.H., 2015. Relationship between gene expression and the accumulation of catechin during spring and autumn in tea plants (*Camellia sinensis* L.). Hort. Res. 2, 15011.

Liu, Y.Z., Wu, K., Huang, J., Liu, Y., Wang, X., Meng, Z.J., Yuan, S.X., Wang, D.X., Luo, J.Y., Zuo, G.W., 2014. The PTEN/PI3K/Akt and Wnt/β-catenin signaling pathways are involved in the inhibitory effect of resveratrol on human colon cancer cell proliferation. Int. J. Oncol. 45(1), 104-112.

López de las Hazas, M.a.C., Mosele, J.I., Macià, A., Ludwig, I.A., Motilva, M.J., 2016. Exploring the colonic metabolism of grape and strawberry anthocyanins and their in vitro apoptotic effects in HT-29 colon cancer cells. J. Agric. Food Chem. 65(31), 6477-6487.

Louis, P., Hold, G.L., Flint, H.J., 2014. The gut microbiota, bacterial metabolites and colorectal cancer. Nat. Rev. Microbiol. 12(10), 661.

Luo, Y., Wang, S.X., Zhou, Z.Q., Wang, Z., Zhang, Y.G., Zhang, Y., Zhao, P., 2014. Apoptotic effect of genistein on human colon cancer cells via inhibiting the nuclear factor-kappa B (NF-κB) pathway. Tumor Biol. 35(11), 11483-11488.

Makris, D.P., Rossiter, J.T., 2001. Domestic processing of onion bulbs (Allium cepa) and asparagus spears (Asparagus officinalis): effect on flavonol content and antioxidant status. J. Agric. Food Chem. 49(7), 3216-3222.

Marín, L., Miguélez, E.M., Villar, C.J., Lombó, F., 2015. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. BioMed Res. Int. 2015.

Marín, M., Giner, R.M., Ríos, J.L., Recio, M.C., 2013. Intestinal anti-inflammatory activity of ellagic acid in the acute and chronic dextrane sulfate sodium models of mice colitis. J. Ethnopharmacol. 150(3), 925-934.

Mariotto, A.B., Robin Yabroff, K., Shao, Y., Feuer, E.J., Brown, M.L., 2011. Projections of the cost of cancer care in the United States: 2010–2020. J. Natl. Cancer Inst. 103(2), 117-128.

Mármol, I., Sánchez-de-Diego, C., Pradilla Dieste, A., Cerrada, E., Rodriguez Yoldi, M.J., 2017. Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. Int. J. Mol. Sci. 18(1), 197.

Martin, S.L., Kala, R., Tollefsbol, T.O., 2018. Mechanisms for the inhibition of colon cancer cells by sulforaphane through epigenetic modulation of microRNA-21 and human telomerase reverse transcriptase (hTERT) down-regulation. Curr. Cancer Drug Targets 18(1), 97-106.

Mazewski, C., Liang, K., de Mejia, E.G., 2018. Comparison of the effect of chemical composition of anthocyanin-rich plant extracts on colon cancer cell proliferation and their potential mechanism of action using in vitro, in silico, and biochemical assays. Food Chem. 242, 378-388.

Megna, B.W., Carney, P.R., Depke, M.G., Nukaya, M., McNally, J., Larsen, L., Rosengren, R.J., Kennedy, G.D., 2017. The aryl hydrocarbon receptor as an antitumor target of synthetic curcuminoids in colorectal cancer. J. Surg. Res. 213, 16-24.

Megna, B.W., Carney, P.R., Nukaya, M., Geiger, P., Kennedy, G.D., 2016. Indole-3-carbinol induces tumor cell death: function follows form. J. Surg. Res. 204(1), 47-54.

Mikkelsen, M.D., Olsen, C.E., Halkier, B.A., 2010. Production of the cancer-preventive glucoraphanin in tobacco. Mol. plant 3(4), 751-759.

Minker, C., Duban, L., Karas, D., JÃ¤rvinen, P.i., Lobstein, A., Muller, C.D., 2015. Impact of procyanidins from different berries on caspase 8 activation in colon cancer. Oxid. Med. Cell Longev. 2015.

Mizushina, Y., Shiomi, K., Kuriyama, I., Takahashi, Y., Yoshida, H., 2013. Inhibitory effects of a major soy isoflavone, genistein, on human DNA topoisomerase II activity and cancer cell proliferation. Int. J. Oncol. 43(4), 1117-1124.

Montgomery, A., Adeyeni, T., San, K., Heuertz, R.M., Ezekiel, U.R., 2016. Curcumin sensitizes silymarin to exert synergistic anticancer activity in colon cancer cells. J. Cancer 7(10), 1250.

Mook, O.R.F., Frederiks, W.M., Van Noorden, C.J.F., 2004. The role of gelatinases in colorectal cancer progression and metastasis. BBA-Rev. Cancer 1705(2), 69-89.

Moriarty, R.M., Naithani, R., Surve, B., 2007. Organosulfur compounds in cancer chemoprevention. Mini-Rev. Med. Chem. 7(8), 827-838.

Morris, J., Moseley, V.R., Cabang, A.B., Coleman, K., Wei, W., Garrett-Mayer, E., Wargovich, M.J., 2016. Reduction in promotor methylation utilizing EGCG (epigallocatechin-3-gallate) restores RXRα expression in human colon cancer cells. Oncotarget 7(23), 35313.

Moseley, V.R., Morris, J., Knackstedt, R.W., Wargovich, M.J., 2013. Green tea polyphenol epigallocatechin 3-gallate, contributes to the degradation of DNMT3A and HDAC3 in HCT 116 human colon cancer cells. Anticancer Res. 33(12), 5325-5333.

Muir, R.M., Ibánez, A.M., Uratsu, S.L., Ingham, E.S., Leslie, C.A., McGranahan, G.H., Batra, N., Goyal, S., Joseph, J., Jemmis, E.D., 2011. Mechanism of gallic acid biosynthesis in bacteria (*Escherichia coli*) and walnut (*Juglansregia*). Plant Mol. Biol. 75(6), 555-565.

Mullen, W., Edwards, C.A., Crozier, A., 2006. Absorption, excretion and metabolite profiling of methyl-, glucuronyl-, glucosyl- and sulpho-conjugates of quercetin in human plasma and urine after ingestion of onions. Br. J. Nutr. 96(1), 107-116.

Murakami, A., Furukawa, I., Miyamoto, S., Tanaka, T., Ohigashi, H., 2013. Curcumin combined with turmerones, essential oil components of turmeric, abolishes inflammation-associated mouse colon carcinogenesis. Biofactors 39(2), 221-232.

Murthy, K.N.C., Jayaprakasha, G.K., Patil, B.S., 2013. Citrus limonoids and curcumin additively inhibit human colon cancer cells. Food Funct. 4(5), 803-810.

Nguyen, A.V., Martinez, M., Stamos, M.J., Moyer, M.P., Planutis, K., Hope, C., Holcombe, R.F., 2009. Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer. Cancer Manag. Res. 1, 25.

Nimptsch, K., Zhang, X., Cassidy, A., Song, M., O'Reilly, É.J., Lin, J.H., Pischon, T., Rimm, E.B., Willett, W.C., Fuchs, C.S., 2015. Habitual intake of flavonoid subclasses and risk of colorectal cancer in 2 large prospective cohorts, 2. Am. J. Clin. Nutr. 103(1), 184-191.

Nirmala, P., Ramanathan, M., 2011. Effect of kaempferol on lipid peroxidation and antioxidant status in 1, 2-dimethyl hydrazine induced colorectal carcinoma in rats. Eur. J. Pharmacol. 654(1), 75-79.

Nomura, A.M.Y., Wilkens, L.R., Murphy, S.P., Hankin, J.H., Henderson, B.E., Pike, M.C., Kolonel, L.N., 2008. Association of vegetable, fruit, and grain intakes with colorectal cancer: the Multiethnic Cohort Study. Am. J. Clin. Nutr. 88(3), 730-737.

Noratto, G.D., Jutooru, I., Safe, S., Angel-Morales, G., Mertens-Talcott, S.U., 2013. The drug resistance suppression induced by curcuminoids in colon cancer SW-480 cells is mediated by reactive oxygen species-induced disruption of the microRNA-27a-ZBTB10-Sp axis. Mol. Nutr. Food Res. 57(9), 1638-1648.

Nuñez-Sánchez, M.A., Dávalos, A., González-Sarrías, A., Casas-Agustench, P., Visioli, F., Monedero-Saiz, T., García-Talavera, N.V., Gómez-Sánchez, M.B., Sánchez-Álvarez, C., García-Albert, A.M., Rodríguez-Gil, F.J., Ruiz-Marín, M., Pastor-Quirante, F.A., Martínez-Díaz, F., Tomás-Barberán, F.A., García-Conesa, M.T., Espín, J.C., 2015. MicroRNAs expression in normal and malignant colon tissues as biomarkers of colorectal cancer and in response to pomegranate extracts consumption: critical issues to discern between modulatory effects and potential artefacts. Mol. Nutr. Food Res. 59(10), 1973-1986.

Nuñez-Sánchez, M.A., García-Villalba, R., Monedero-Saiz, T., García-Talavera, N.V., Gómez-Sánchez, M.B., Sánchez-Álvarez, C., García-Albert, A.M., Rodríguez-Gil, F.J., Ruiz-Marín, M., Pastor-Quirante, F.A., Martínez-Díaz, F., 2014. Targeted metabolic profiling of pomegranate polyphenols and urolithins in plasma, urine and colon tissues from colorectal cancer patients. Mol. Nutr. Food Res. 58(6), 1199-1211.

Nuñez-Sánchez, M.A., González-Sarrías, A., García-Villalba, R., Monedero-Saiz, T., García-Talavera, N.V., Gómez-Sánchez, M.B., Sánchez-Álvarez, C., García-Albert, A.M., Rodríguez-Gil, F.J., Ruiz-Marín, M., Pastor-Quirante, F.A., 2017. Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: a randomized clinical trial. J. Nutr. Biochem. 42, 126-133.

Núñez-Sánchez, M.A., González-Sarrías, A., Romo-Vaquero, M., García-Villalba, R., Selma, M.V., Tomás-Barberán, F.A., García-Conesa, M.T., Espín, J.C., 2015. Dietary phenolics against colorectal cancer-From promising preclinical results to poor translation into clinical trials: Pitfalls and future needs. Mol. Nutr. Food Res. 59(7), 1274-1291.

Oh, S., Gwak, J., Park, S., Yang, C.S., 2014. Green tea polyphenol EGCG suppresses Wnt/β-catenin signaling by promoting GSK-3β-and PP2A-independent β-catenin phosphorylation/degradation. Biofactors 40(6), 586-595.

Ohta, T., Takahashi, M., Ochiai, A., 2006. Increased protein expression of both inducible nitric oxide synthase and cyclooxygenase-2 in human colon cancers. Cancer Lett. 239(2), 246-253.

Ooko, E., Kadioglu, O., Greten, H.J., Efferth, T., 2017. Pharmacogenomic Characterization and Isobologram Analysis of the Combination of Ascorbic Acid and Curcumin—Two Main Metabolites of Curcuma longa—in Cancer Cells. Front. Pharmacol. 8, 38.

Ozdal, T., Sela, D.A., Xiao, J., Boyacioglu, D., Chen, F., Capanoglu, E., 2016. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. Nutrients 8(2), 78.

Panaro, M.A., Carofiglio, V., Acquafredda, A., Cavallo, P., Cianciulli, A., 2012. Anti-inflammatory effects of resveratrol occur via inhibition of lipopolysaccharide-induced NF-κB activation in Caco-2 and SW480 human colon cancer cells. Br. J. Nutr. 108(9), 1623-1632.

Pandey, K.B., Rizvi, S.I., 2009. Plant polyphenols as dietary antioxidants in human health and disease. Oxid. Med. Cell Longev. 2(5), 270-278.

Pandurangan, A.K., Mohebali, N., Esa, N.M., Looi, C.Y., Ismail, S., Saadatdoust, Z., 2015. Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: Possible mechanisms. Int. Immunopharmacol. 28(2), 1034-1043.

Papi, A., Farabegoli, F., Iori, R., Orlandi, M., De Nicola, G.R., Bagatta, M., Angelino, D., Gennari, L., Ninfali, P., 2013. Vitexin-2-O-xyloside, raphasatin and (−)-epigallocatechin-3-gallate synergistically affect cell growth and apoptosis of colon cancer cells. Food Chem. 138(2-3), 1521-1530.

Park, M.H., Kim, J.H., Chung, Y.H., Lee, S.H., 2016. Bakuchiol sensitizes cancer cells to TRAIL through ROS-and JNK-mediated upregulation of death receptors and downregulation of survival proteins. Biochem. Biophys. Res. Commun. 473(2), 586-592.

Park, S.Y., Jung, C.H., Song, B., Park, O.J., Kim, Y.M., 2013. Pro-apoptotic and migration-suppressing potential of EGCG, and the involvement of AMPK in the p53-mediated modulation of VEGF and MMP-9 expression. Oncol. Lett. 6(5), 1346-1350.

Patel, K.R., Brown, V.A., Jones, D.J.L., Britton, R.G., Hemingway, D., Miller, A.S., West, K.P., Booth, T.D., Perloff, M., Crowell, J.A., 2010. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res. 70(19), 7392-7399.

Patel, K.R., Scott, E., Brown, V.A., Gescher, A.J., Steward, W.P., Brown, K., 2011. Clinical trials of resveratrol. Ann. N. Y. Acad. Sci. 1215(1), 161-169.

Pino, M.S., Chung, D.C., 2010. The chromosomal instability pathway in colon cancer. Gastroenterology 138(6), 2059-2072.

Petersen, M., Abdullah, Y., Benner, J., Eberle, D., Gehlen, K., HÃ¼cherig, S., Janiak, V., Kim, K.H., Sander, M., Weitzel, C., 2009. Evolution of rosmarinic acid biosynthesis. Phytochemistry 70(15-16), 1663-1679.

Pisha, E., Chai, H., Lee, I.S., Chagwedera, T.E., Farnsworth, N.R., Cordell, G.A., Beecher, C.W.W., Fong, H.H.S., Kinghorn, A.D., Brown, D.M., 1995. Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. Nat. Med. 1(10), 1046.

Polycarpou, E., Meira, L.B., Carrington, S., Tyrrell, E., Modjtahedi, H., Carew, M.A., 2013. Resveratrol 3-O-d-glucuronide and resveratrol 4′-O-d-glucuronide inhibit colon cancer cell growth: Evidence for a role of A3 adenosine receptors, cyclin D1 depletion, and G1 cell cycle arrest. Mol. Nutr. Food Res. 57(10), 1708-1717.

Prasad, S., Yadav, V.R., Sung, B., Reuter, S., Kannappan, R., Deorukhkar, A., Diagaradjane, P., Wei, C., Baladandayuthapani, V., Krishnan, S., 2012. Ursolic acid inhibits growth and metastasis of human colorectal cancer in an orthotopic nude mouse model by targeting multiple cell signaling pathways: chemosensitization with capecitabine. Clin. Cancer Res. 18(18), 4942-4953.

Qiu, P., Xu, L., Gao, L., Zhang, M., Wang, S., Tong, S., Sun, Y., Zhang, L., Jiang, T., 2013. Exploring pyrimidine-substituted curcumin analogues: design, synthesis and effects on EGFR signaling. Bioorganic Med. Chem. 21(17), 5012-5020.

Raja, S.B., Rajendiran, V., Kasinathan, N.K., Amrithalakshmi, P., Venkatabalasubramanian, S., Murali, M.R., Devaraj, H., Devaraj, S.N., 2017. Differential cytotoxic activity of Quercetin on colonic cancer cells depends on ROS generation through COX-2 expression. Food Chem. Toxicol. 106, 92-106.

Rajitha, B., Nagaraju, G.P., Shaib, W.L., Alese, O.B., Snyder, J.P., Shoji, M., Pattnaik, S., Alam, A., El-Rayes, B.F., 2017. Novel synthetic curcumin analogs as potent antiangiogenic agents in colorectal cancer. Mol. Carcinog. 56(1), 288-299.

Ramamoorthi, G., Sivalingam, N., 2014. Molecular mechanism of TGF-β signaling pathway in colon carcinogenesis and status of curcumin as chemopreventive strategy. Tumor Biol. 35(8), 7295-7305.

Ramos, S., 2008. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. Mol. Nutr. Food Res. 52(5), 507-526.

Rana, C., Piplani, H., Vaish, V., Nehru, B., Sanyal, S.N., 2015a. Downregulation of PI3-K/Akt/PTEN pathway and activation of mitochondrial intrinsic apoptosis by Diclofenac and Curcumin in colon cancer. Mol. Cell. Biochem. 402(1-2), 225-241.

Rana, C., Piplani, H., Vaish, V., Nehru, B., Sanyal, S.N., 2015b. Downregulation of telomerase activity by diclofenac and curcumin is associated with cell cycle arrest and induction of apoptosis in colon cancer. Tumor Biol. 36(8), 5999-6010.

Reddivari, L., Charepalli, V., Radhakrishnan, S., Vadde, R., Elias, R.J., Lambert, J.D., Vanamala, J.K.P., 2016. Grape compounds suppress colon cancer stem cells in vitro and in a rodent model of colon carcinogenesis. BMC Complement. Altern. Med. 16(1), 278.

Reed, G.A., Peterson, K.S., Smith, H.J., Gray, J.C., Sullivan, D.K., Mayo, M.S., Crowell, J.A., Hurwitz, A., 2005. A phase I study of indole-3-carbinol in women: tolerability and effects. Cancer Epidemiol. Biomarkers Prev. 14(8), 1953-1960.

Refolo, M.G., D'Alessandro, R., Malerba, N., Laezza, C., Bifulco, M., Messa, C., Caruso, M.G., Notarnicola, M., Tutino, V., 2015. Anti proliferative and pro apoptotic effects of flavonoid quercetin are mediated by CB1 receptor in human colon cancer cell lines. J. Cell. Physiol. 230(12), 2973-2980.

Ricciardiello, L., Bazzoli, F., Fogliano, V., 2011. Phytochemicals and colorectal cancer prevention—myth or reality? Nat. Rev. Gastroenterol. Hepatol. 8(10), 592.

Roberts, A.T., Martin, C.K., Liu, Z., Amen, R.J., Woltering, E.A., Rood, J.C., Caruso, M.K., Yu, Y., Xie, H., Greenway, F.L., 2007. The safety and efficacy of a dietary herbal supplement and gallic acid for weight loss. J. Med. Food 10(1), 184-188.

Rodrigues, N.R., Rowan, A., Smith, M.E., Kerr, I.B., Bodmer, W.F., Gannon, J.V., Lane, D.P., 1990. p53 mutations in colorectal cancer. Proc. Natl. Acad. Sci. U.S.A. 87(19), 7555-7559.

Roowi, S., Stalmach, A., Mullen, W., Lean, M.E.J., Edwards, C.A., Crozier, A., 2009. Green tea flavan-3-ols: colonic degradation and urinary excretion of catabolites by humans. J. Agric. Food Chem. 58(2), 1296-1304.

Roy, S., Levi, E., Majumdar, A.P.N., Sarkar, F.H., 2012. Expression of miR-34 is lost in colon cancer which can be re-expressed by a novel agent CDF. J. Hematol. Oncol. 5(1), 58.

Roy, S., Yu, Y., Padhye, S.B., Sarkar, F.H., Majumdar, A.P.N., 2013. Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. PLoS One 8(7), e68543.

Saldanha, S.N., Kala, R., Tollefsbol, T.O., 2014. Molecular mechanisms for inhibition of colon cancer cells by combined epigenetic-modulating epigallocatechin gallate and sodium butyrate. Exp. Cell Res. 324(1), 40-53.

San Hipólito-Luengo, Á., Alcaide, A., Ramos-González, M., Cercas, E., Vallejo, S., Romero, A., Talero, E., Sánchez-Ferrer, C.F., Motilva, V., Peiró, C., 2017. Dual Effects of Resveratrol on Cell Death and Proliferation of Colon Cancer Cells. Nutr. Cancer 69(7), 1019-1027.

Sangeetha, N., Nalini, N., 2015. Silibinin modulates caudal-type homeobox transcription factor (CDX2), an intestine specific tumor suppressor to abrogate colon cancer in experimental rats. Hum. Exp. Toxicol. 34(1), 56-64.

Sankpal, U.T., Nagaraju, G.P., Gottipolu, S.R., Hurtado, M., Jordan, C.G., Simecka, J.W., Shoji, M., El-Rayes, B., Basha, R., 2016. Combination of tolfenamic acid and curcumin induces colon cancer cell growth

inhibition through modulating specific transcription factors and reactive oxygen species. Oncotarget 7(3), 3186.

Santos, I.S., Ponte, B.M., Boonme, P., Silva, A.M., Souto, E.B., 2013. Nanoencapsulation of polyphenols for protective effect against colon–rectal cancer. Biotechnol. Adv. 31(5), 514-523.

Sato, T., Higuchi, Y., Shibagaki, Y., Hattori, S., 2017. Phosphoproteomic Analysis Identifies Signaling Pathways Regulated by Curcumin in Human Colon Cancer Cells. Anticancer Res. 37(9), 4789-4798.

Saud, S.M., Li, W., Morris, N.L., Matter, M.S., Colburn, N.H., Kim, Y.S., Young, M.R., 2014. Resveratrol prevents tumorigenesis in mouse model of Kras activated sporadic colorectal cancer by suppressing oncogenic Kras expression. Carcinogenesis 35(12), 2778-2786.

Schmoll, H.J., Van Cutsem, E., Stein, A., Valentini, V., Glimelius, B., Haustermans, K., Nordlinger, B., Van de Velde, C.J., Balmana, J., Regula, J., 2012. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann. Oncol. 23(10), 2479-2516.

Schnekenburger, M., Dicato, M., Diederich, M., 2014. Plant-derived epigenetic modulators for cancer treatment and prevention. Biotechnol. Adv. 32(6), 1123-1132.

Seeram, N.P., Henning, S.M., Zhang, Y., Suchard, M., Li, Z., Heber, D., 2006. Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 hours. J. Nutr. 136(10), 2481-2485.

Sekar, V., Anandasadagopan, S.K., Ganapasam, S., 2016. Genistein regulates tumor microenvironment and exhibits anticancer effect in dimethyl hydrazine-induced experimental colon carcinogenesis. BioFactors 42(6), 623-637.

Shafiee, G., Saidijam, M., Tavilani, H., Ghasemkhani, N., Khodadadi, I., 2016. Genistein induces apoptosis and inhibits proliferation of HT29 colon cancer cells. Int. J. Mol. Cell. Med. 5(3), 178.

Shakibaei, M., Kraehe, P., Popper, B., Shayan, P., Goel, A., Buhrmann, C., 2015. Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer. BMC Cancer 15(1), 250.

Shakibaei, M., Mobasheri, A., Lueders, C., Busch, F., Shayan, P., Goel, A., 2013. Curcumin enhances the effect of chemotherapy against colorectal cancer cells by inhibition of NF-κB and Src protein kinase signaling pathways. PLoS One 8(2), e57218.

Shan, J.Z., Huang, J.J., Zhang, Q., Xuan, Y.Y., 2016. Ursolic acid sensitized colon cancer cells to chemotherapy under hypoxia by inhibiting MDR1 through HIF-1α. J. Zhejiang Univ. 17, 672-682.

Shannon, J., White, E., Shattuck, A.L., Potter, J.D., 1996. Relationship of food groups and water intake to colon cancer risk. Cancer Epidemiol. Biomarkers Prev. 5(7), 495-502.

Sharma, R.A., Euden, S.A., Platton, S.L., Cooke, D.N., Shafayat, A., Hewitt, H.R., Marczylo, T.H., Morgan, B., Hemingway, D., Plummer, S.M., 2004. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin. Cancer Res. 10(20), 6847-6854.

Shehzad, A., Lee, J., Huh, T.L., Lee, Y.S., 2013. Curcumin induces apoptosis in human colorectal carcinoma (HCT-15) cells by regulating expression of Prp4 and p53. Mol. Cells 35(6), 526-532.

Shimizu, M., Fukutomi, Y., Ninomiya, M., Nagura, K., Kato, T., Araki, H., Suganuma, M., Fujiki, H., Moriwaki, H., 2008. Green tea extracts for the prevention of metachronous colorectal adenomas: a pilot study. Cancer Epidemiol. Biomarkers Prev. 17(11), 3020-3025.

Shin, C.M., Lee, D.H., Seo, A.Y., Lee, H.J., Kim, S.B., Son, W.C., Kim, Y.K., Lee, S.J., Park, S.H., Kim, N., 2017. Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: a randomized clinical trial. Clin. Nutr.

Shin, D.Y., Lu, J.N., Kim, G.Y., Jung, J.M., Kang, H.S., Lee, W.S., Choi, Y.H., 2011. Anti-invasive activities of anthocyanins through modulation of tight junctions and suppression of matrix metalloproteinase activities in HCT-116 human colon carcinoma cells. Oncol. Rep. 25(2), 567-572.

Siegel, R.L., Miller, K.D., Jemal, A., 2016. Cancer statistics, 2016. CA Cancer J. Clin. 66(1), 7-30.

Simons, C.C.J.M., Hughes, L.A.E., Arts, I.C.W., Goldbohm, R.A., van den Brandt, P.A., Weijenberg, M.P., 2009. Dietary flavonol, flavone and catechin intake and risk of colorectal cancer in the Netherlands Cohort Study. Int. J. Cancer 125(12), 2945-2952.

Singh, K., Connors, S.L., Macklin, E.A., Smith, K.D., Fahey, J.W., Talalay, P., Zimmerman, A.W., 2014. Sulforaphane treatment of autism spectrum disorder (ASD). Proc. Natl. Acad. Sci. U.S.A. 111(43), 15550-15555.

Smith, G., Carey, F.A., Beattie, J., Wilkie, M.J.V., Lightfoot, T.J., Coxhead, J., Garner, R.C., Steele, R.J.C., Wolf, C.R., 2002. Mutations in APC, Kirsten-ras, and p53—alternative genetic pathways to colorectal cancer. Proc. Natl. Acad. Sci. U.S.A. 99(14), 9433-9438.

Stewart, A.J., Bozonnet, S., Mullen, W., Jenkins, G.I., Lean, M.E.J., Crozier, A., 2000. Occurrence of flavonols in tomatoes and tomato-based products. J. Agric. Food Chem. 48(7), 2663-2669.

Stoner, G.D., Sardo, C., Apseloff, G., Mullet, D., Wargo, W., Pound, V., Singh, A., Sanders, J., Aziz, R., Casto, B., 2005. Pharmacokinetics of Anthocyanins and Ellagic Acid in Healthy Volunteers Fed Freeze-Dried Black Raspberries Daily for 7 Days. J. Clin. Pharmacol. 45(10), 1153-1164.

Subramanian, A.P., Jaganathan, S.K., Mandal, M., Supriyanto, E., Muhamad, I.I., 2016. Gallic acid induced apoptotic events in HCT-15 colon cancer cells. World J. Gastroenterol. 22(15), 3952.

Sufi, S.A., Adigopula, L.N., Syed, S.B., Mukherjee, V., Coumar, M.S., Rao, H.S.P., Rajagopalan, R., 2017. In-silico and in-vitro anti-cancer potential of a curcumin analogue (1E, 6E)-1, 7-di (1H-indol-3-yl) hepta-1, 6-diene-3, 5-dione. Biomed. Pharmacother. 85, 389-398.

Sultana, B., Anwar, F., 2008. Flavonols (kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. Food Chem. 108(3), 879-884.

Sun, Y., Wu, X., Cai, X., Song, M., Zheng, J., Pan, C., Qiu, P., Zhang, L., Zhou, S., Tang, Z., 2016. Identification of pinostilbene as a major colonic metabolite of pterostilbene and its inhibitory effects on colon cancer cells. Mol. Nutr. Food Res. 60(9), 1924-1932.

Tang, H., Yao, X., Yao, C., Zhao, X., Zuo, H., Li, Z., 2017. Anti-colon cancer effect of caffeic acid *p*-nitrophenethyl ester *in vitro* and *in vivo* and detection of its metabolites. Sci. Rep. 7(1), 7599.

Terzić, J., Grivennikov, S., Karin, E., Karin, M., 2010. Inflammation and colon cancer. Gastroenterology 138(6), 2101-2114. e2105.

Tewari, D., Stankiewicz, A.M., Mocan, A., Sah, A.N., Tzvetkov, N., Huminiecki, L., HorbaÅ„czuk, J.a.O., Atanasov, A.G., 2018. Ethnopharmacological approaches for dementia therapy and significance of natural products and herbal drugs. Front. Aging Neurosci. 10, 3.

Thomasset, S., Berry, D.P., Cai, H., West, K., Marczylo, T.H., Marsden, D., Brown, K., Dennison, A., Garcea, G., Miller, A., 2009. Pilot study of oral anthocyanins for colorectal cancer chemoprevention. Cancer Prev. Res. 2(7), 625-633.

Tong, W., Wang, Q., Sun, D., Suo, J., 2016. Curcumin suppresses colon cancer cell invasion via AMPK-induced inhibition of NF-κB, uPA activator and MMP9. Oncol. Lett. 12(5), 4139-4146.

Tsai, C.C., Chuang, T.W., Chen, L.J., Niu, H.S., Chung, K.M., Cheng, J.T., Lin, K.C., 2015. Increase in apoptosis by combination of metformin with silibinin in human colorectal cancer cells. World J. Gastroenterol. 21(14), 4169.

Umesalma, S., Nagendraprabhu, P., Sudhandiran, G., 2014. Antiproliferative and apoptotic-inducing potential of ellagic acid against 1, 2-dimethyl hydrazine-induced colon tumorigenesis in Wistar rats. Mol. Cell. Biochem. 388(1-2), 157-172.

Umesalma, S., Nagendraprabhu, P., Sudhandiran, G., 2015. Ellagic acid inhibits proliferation and induced apoptosis via the Akt signaling pathway in HCT-15 colon adenocarcinoma cells. Mol. Cell. Biochem. 399(1-2), 303-313.

van Duijnhoven, F.J., Bueno-De-Mesquita, H.B., Ferrari, P., Jenab, M., Boshuizen, H.C., Ros, M.M., Casagrande, C., Tjonneland, A., Olsen, A., Overvad, K., Thorlacius-Ussing, O., Clavel-Chapelon, F., Boutron-Ruault, M., Morois, S., Kaaks, R., Linseisen, J., Boeing, H., Nothlings, U., Trichopoulou, A., Trichopoulos, D., Misirli, G., Palli, D., Sieri, S., Panico, S., Tumino, R., Vineis, P., Peeters, P., van Gils,

C., Ocke, M., Lund, E., Engeset, D., Skeie, G., Suarez, L., Gonzalez, C., Sanchez, M., Dorronsoro, M., Navarro, C., Barricarte, A., Berglund, G., Manjer, J., Hallmans, G., Palmqvist, R., Bingham, S., Khaw, K., Key, T., Allen, N., Boffetta, P., Slimani, N., Rinaldi, S., Gallo, V., Norat, T., Riboli, E., 2009. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. Am. J. Clin. Nutr. 89(5), 1441-1452.

Venancio, V.P., Cipriano, P.A., Kim, H., Antunes, L.n.M.G., Talcott, S.T., Mertens-Talcott, S.U., 2017. Cocoplum (*Chrysobalanus icaco* L.) anthocyanins exert anti-inflammatory activity in human colon cancer and non-malignant colon cells. Food Funct. 8(1), 307-314.

Venkatachalam, K., Gunasekaran, S., Jesudoss, V.A.S., Namasivayam, N., 2013. The effect of rosmarinic acid on 1, 2-dimethylhydrazine induced colon carcinogenesis. Exp. Toxicol. Pathol. 65(4), 409-418.

Venkatachalam, K., Gunasekaran, S., Namasivayam, N., 2016. Biochemical and molecular mechanisms underlying the chemopreventive efficacy of rosmarinic acid in a rat colon cancer. Eur. J. Pharmacol. 791, 37-50.

Vivanco, I., Sawyers, C.L., 2002. The phosphatidylinositol 3-kinase–AKT pathway in human cancer. Nat. Rev. Cancer 2(7), 489.

Vogelstein, B., Fearon, E.R., Hamilton, S.R., Kern, S.E., Preisinger, A.C., Leppert, M., Smits, A.M.M., Bos, J.L., 1988. Genetic alterations during colorectal-tumor development. N. Engl. J. Med. 319(9), 525-532.

Waghela, B.N., Sharma, A., Dhumale, S., Pandey, S.M., Pathak, C., 2015. Curcumin conjugated with PLGA potentiates sustainability, anti-proliferative activity and apoptosis in human colon carcinoma cells. PLoS One 10(2), e0117526.

Wang, H., Li, Q., Chen, H., 2012. Genistein affects histone modifications on Dickkopf-related protein 1 (DKK1) gene in SW480 human colon cancer cell line. PLoS One 7(7), e40955.

Wang, J., Guo, W., Chen, W., Yu, W., Tian, Y., Fu, L., Shi, D., Tong, B., Xiao, X., Huang, W., 2013a. Melatonin potentiates the antiproliferative and pro-apoptotic effects of ursolic acid in colon cancer cells by modulating multiple signaling pathways. J. Pineal Res. 54(4), 406-416.

Wang, J., Liu, L., Qiu, H., Zhang, X., Guo, W., Chen, W., Tian, Y., Fu, L., Shi, D., Cheng, J., 2013b. Ursolic acid simultaneously targets multiple signaling pathways to suppress proliferation and induce apoptosis in colon cancer cells. PLoS One 8(5), e63872.

Wang, J., Zhang, J., Zhang, C.J., Wong, Y.K., Lim, T.K., Hua, Z.C., Liu, B., Tannenbaum, S.R., Shen, H.M., Lin, Q., 2016. In situ proteomic profiling of curcumin targets in HCT116 colon cancer cell line. Sci. Rep. 6, 22146.

Wang, J.Y., Chang, C.C., Chiang, C.C., Chen, W.M., Hung, S.C., 2012. Silibinin suppresses the maintenance of colorectal cancer stem-like cells by inhibiting PP2A/AKT/mTOR pathways. J. Cell. Biochem. 113(5), 1733-1743.

Wang, L.S., Kuo, C.T., Cho, S.J., Seguin, C., Siddiqui, J., Stoner, K., Weng, Y.I., Huang, T.H.M., Tichelaar, J., Yearsley, M., 2013. Black raspberry-derived anthocyanins demethylate tumor suppressor genes through the inhibition of DNMT1 and DNMT3B in colon cancer cells. Nutr. Cancer 65(1), 118-125.

Wang, M., Chen, S., Qing, Y., Wu, D., Lin, Y.M., Chen, J., Li, Y.Q., 2013. Effects of autophagy modulator on autophagy and uridine 5'-diphospho-glucuronosyltransferase 1A1 induced by sulforaphane. J. Med. Sci. 93(8), 614-618.

Wang, M., Chen, S., Wang, S., Sun, D., Chen, J., Li, Y., Han, W., Yang, X., Gao, H.Q., 2012. Effects of phytochemicals sulforaphane on uridine diphosphate-glucuronosyltransferase expression as well as cell-cycle arrest and apoptosis in human colon cancer Caco-2 cells. Chin. J. Physiol. 55(2), 134-144.

Wang, M., Zhu, J.Y., Chen, S., Qing, Y., Wu, D., Lin, Y.M., Luo, J.Z., Han, W., Li, Y.Q., 2014. Effects of co-treatment with sulforaphane and autophagy modulators on uridine 5'-diphospho-glucuronosyltransferase 1A isoforms and cytochrome P450 3A4 expression in Caco-2 human colon cancer cells. Oncol. Lett. 8(6), 2407-2416.

Wang, S., Liu, Z., Wang, L., Zhang, X., 2009. NF-κB signaling pathway, inflammation and colorectal cancer. Cell. Mol. Immunol. 6(5), 327.

Wang, Y., Lu, P., Zhang, W., Du, Q., Tang, J., Wang, H., Lu, J., Hu, R., 2016. GEN-27, a newly synthetic isoflavonoid, inhibits the proliferation of colon cancer cells in inflammation microenvironment by suppressing NF-κB pathway. Mediators Inflamm. 2016(Article ID 2853040), 1-17.

Watts, K.T., Lee, P.C., Schmidt-Dannert, C., 2006. Biosynthesis of plant-specific stilbene polyketides in metabolically engineered *Escherichia coli*. BMC Biotechnol. 6(1), 22.

Wittemer, S.M., Ploch, M., Windeck, T., Müller, S.C., Drewelow, B., Derendorf, H., Veit, M., 2005. Bioavailability and pharmacokinetics of caffeoylquinic acids and flavonoids after oral administration of Artichoke leaf extracts in humans. Phytomedicine 12(1-2), 28-38.

Woo, S.M., Min, K.J., Kim, S., Park, J.W., Kim, D.E., Chun, K.S., Kim, Y.H., Lee, T.J., Kim, S.H., Choi, Y.H., 2014. Silibinin induces apoptosis of HT29 colon carcinoma cells through early growth response-1 (EGR-1)-mediated non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) up-regulation. Chem.-Biol. Interact. 211, 36-43.

Wu, X., Pfalzer, A.C., Koh, G.Y., Tang, S., Crott, J.W., Thomas, M.J., Meydani, M., Mason, J.B., 2017. Curcumin and Salsalate Suppresses Colonic Inflammation and Procarcinogenic Signaling in High-Fat-Fed, Azoxymethane-Treated Mice. J. Agric. Food Chem. 65(33), 7200-7209.

Xiao, L., Mertens, M., Wortmann, L., Kremer, S., Valldor, M., Lammers, T., Kiessling, F., Mathur, S., 2015. Enhanced in vitro and in vivo cellular imaging with green tea coated water-soluble iron oxide nanocrystals. ACS Appl. Mater. Interfaces 7(12), 6530-6540.

Xie, J., Yang, Z., Zhou, C., Zhu, J., Lee, R.J., Teng, L., 2016. Nanotechnology for the delivery of phytochemicals in cancer therapy. Biotechnol. Adv. 34(4), 343-353.

Xu, B., Yu, L., Zhao, L.Z., 2017. Curcumin up regulates T helper 1 cells in patients with colon cancer. Am. J. Transl. Res. 9(4), 1866.

Xuan, L., Jiang, R., Wu, Z., Yi, H., Yao, C., Hou, Q., Qu, C., 2016. Vam3, a Compound Derived from Vitis amurensis Rupr., Attenuated Colitis-Related Tumorigenesis by Inhibiting NF-κB Signaling Pathway. Front. Pharmacol. 7, 311.

Yang, J.Y., Zhong, X., Yum, H.W., Lee, H.J., Kundu, J.K., Na, H.K., Surh, Y.J., 2013. Curcumin inhibits STAT3 signaling in the colon of dextran sulfate sodium-treated mice. j. Cancer Prev. 18(2), 186.

Yang, L., Liu, Y., Wang, M., Qian, Y., Dong, X., Gu, H., Wang, H., Guo, S., Hisamitsu, T., 2016. Quercetin-induced apoptosis of HT-29 colon cancer cells via inhibition of the Akt-CSN6-Myc signaling axis. Mol. Med. Rep. 14(5), 4559-4566.

Yang, X., Li, Z., Wu, Q., Chen, S., Yi, C., Gong, C., 2017. TRAIL and curcumin codelivery nanoparticles enhance TRAIL-induced apoptosis through upregulation of death receptors. Drug Deliv. 24(1), 1526-1536.

Yim, S.H., Kim, H.J., Park, S.H., Kim, J., Williams, D.R., Jung, D.W., Lee, I.S., 2012. Cytotoxic caffeic acid derivatives from the rhizomes of *Cimicifuga heracleifolia*. Arch. Pharm. Res. 35(9), 1559-1565.

Yousef, A.I., El-Masry, O.S., Abdel Mohsen, M.A., 2016a. Impact of cellular genetic make-up on colorectal cancer cell lines response to ellagic acid: implications of small interfering RNA. Asian Pac. J. Cancer. Prev. 17(2), 743-748.

Yousef, A.I., El-Masry, O.S., Yassin, E.H., 2016b. The anti-oncogenic influence of ellagic acid on colon cancer cells in leptin-enriched microenvironment. Tumor Biol. 37(10), 13345-13353.

Yu, Y., Sarkar, F.H., Majumdar, A.P.N., 2013. Down-regulation of miR-21 induces differentiation of chemoresistant colon cancer cells and enhances susceptibility to therapeutic regimens. Transl. Oncol. 6(2), 180-186.

Yuan, S.X., Wang, D.X., Wu, Q.X., Ren, C.M., Li, Y., Chen, Q.Z., Zeng, Y.H., Shao, Y., Yang, J.-Q., Bai, Y., 2016. BMP9/p38 MAPK is essential for the antiproliferative effect of resveratrol on human colon cancer. Oncol. Rep. 35(2), 939-947.

Zang, Y.X., Kim, J.H., Park, Y.D., Kim, D.H., Hong, S.B., 2008. Metabolic engineering of aliphatic glucosinolates in Chinese cabbage plants expressing Arabidopsis MAM1, CYP79F1, and CYP83A1. BMB reports 41(6), 472-478.

Zhang, J., Feng, Z., Wang, C., Zhou, H., Liu, W., Kanchana, K., Dai, X., Zou, P., Gu, J., Cai, L., 2017. Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. Am. J. Cancer Res. 7(2), 275.

Zhang, J., Wang, J., Xu, J., Lu, Y., Jiang, J., Wang, L., Shen, H.M., Xia, D., 2016. Curcumin targets the TFEB-lysosome pathway for induction of autophagy. Oncotarget 7(46), 75659.

Zhang, X.A., Zhang, S., Yin, Q., Zhang, J., 2015. Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway. Pharmacogn. Mag. 11(42), 404.

Zhang, Y., Butelli, E., Martin, C., 2014. Engineering anthocyanin biosynthesis in plants. Curr. Opin. Plant Biol. 19, 81-90.

Zhang, Y., Li, Q., Zhou, D., Chen, H., 2013. Genistein, a soya isoflavone, prevents azoxymethane-induced up-regulation of WNT/β-catenin signalling and reduces colon pre-neoplasia in rats. Br. J. Nutr. 109(1), 33-42.

Zhang, Z., Chen, H., Xu, C., Song, L., Huang, L., Lai, Y., Wang, Y., Chen, H., Gu, D., Ren, L., 2016. Curcumin inhibits tumor epithelial-mesenchymal transition by downregulating the Wnt signaling pathway and upregulating NKD2 expression in colon cancer cells. Oncol. Rep. 35(5), 2615-2623.

Zhang, Z., Wang, C.Z., Du, G.J., Qi, L.W., Calway, T., He, T.C., Du, W., Yuan, C.S., 2013. Genistein induces G2/M cell cycle arrest and apoptosis via ATM/p53-dependent pathway in human colon cancer cells. Int. J. Oncol. 43(1), 289-296.

Zhao, H., Liu, Q., Wang, S., Dai, F., Cheng, X., Cheng, X., Chen, W., Zhang, M., Chen, D., 2017. In vitro additive antitumor effects of dimethoxycurcumin and 5-fluorouracil in colon cancer cells. Cancer Med. 6(7), 1698-1706.

Zhao, J., Li, G., Bo, W., Zhou, Y., Dang, S., Wei, J., Li, X., Liu, M., 2017. Multiple effects of ellagic acid on human colorectal carcinoma cells identified by gene expression profile analysis. Int. J. Oncol. 50(2), 613-621.

Zhao, Y., Fan, D., Zheng, Z.P., Li, E.T.S., Chen, F., Cheng, K.W., Wang, M., 2017. 8-C-(E-phenylethenyl) quercetin from onion/beef soup induces autophagic cell death in colon cancer cells through ERK activation. Mol. Nutr. Food Res. 61(2), 1600437.

Zhou, F., Zhou, H., Wang, T., Mu, Y., Wu, B., Guo, D.L., Zhang, X.M., Wu, Y., 2012. Epigallocatechin-3-gallate inhibits proliferation and migration of human colon cancer SW620 cells in vitro. Acta Pharmacol. Sin. 33(1), 120.

Zhu, J., Bultynck, G., Luyten, T., Parys, J.B., Creemers, J.W.M., Van de Ven, W.J.M., Vermorken, A.J.M., 2013. Curcumin affects proprotein convertase activity: Elucidation of the molecular and subcellular mechanism. BBA-Mol. Cell Res. 1833(8), 1924-1935.

Zhu, Z., Qian, Z., Yan, Z., Zhao, C., Wang, H., Ying, G., 2013. A phase I pharmacokinetic study of ursolic acid nanoliposomes in healthy volunteers and patients with advanced solid tumors. Int. J. Nnanomedicine 8, 129.

Figure legends

Fig. 1. Dietary phytochemicals can modulate key signaling pathways by targeting different stages of CRC from initiation to progression.

Fig. 2. Dietary phytochemicals target MAPK signaling pathway, inducing chemopreventive effects on CRC.The symbol (↑) denotes increasing activity and (perpendicular) suppressing activity.

Fig. 3. Dietary phytochemicals target NF-κB signaling pathway, inducing chemopreventive effects on CRC.The symbol (perpendicular) denotes suppressing activity.

Fig. 4. Dietary phytochemicals arrest cell cycle in different phase of CRC.The symbol (perpendicular) denotes suppressing activity, (↑) increasing activity and (↓) decreasing activity.

Fig. 5. Dietary phytochemicals target Wnt/β-catenin signaling pathway, inducing chemopreventive effects on CRC.The symbol (perpendicular) denotes suppressing activity.

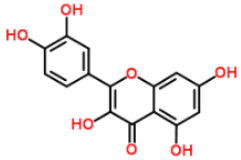
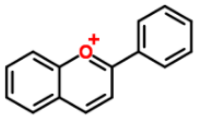
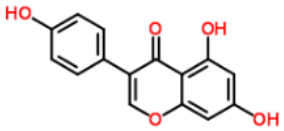
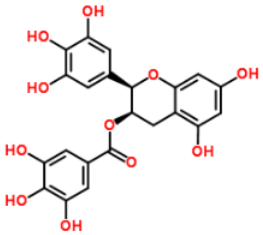
Fig. 6. Dietary phytochemicals target PI3K/Akt signaling pathway, inducing chemopreventive effects on CRC.The symbol (perpendicular) denotes suppressing activity.

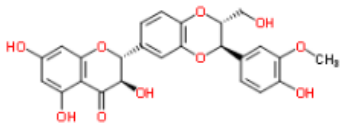
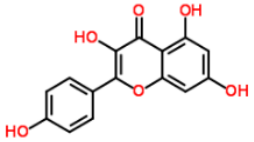
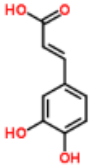
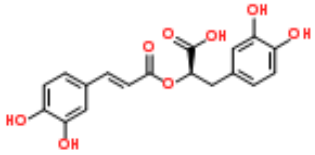
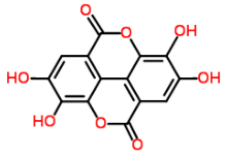
Fig. 7. Dietary phytochemicals target STAT1-STAT3 signaling pathway, inducing chemopreventive effects on CRC.The symbol (perpendicular) denotes suppressing activity.

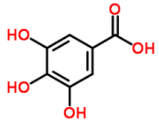
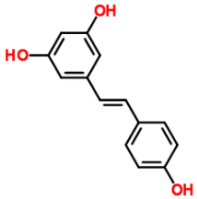
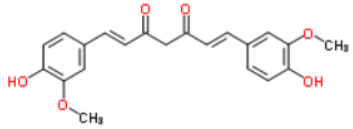
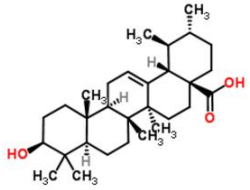
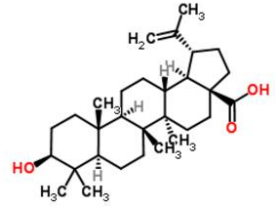
Fig. 8. Epigenetic modifications by dietary phytochemicals target DNA methylation, histone modifications and miRNA-mediated alteration. The symbol (perpendicular) denotes suppressing activity and (↑) increasing activity.

Table 1

The most common dietary phytochemicals with their representative sources and intestinal metabolites.

Dietary phytochemicals	Representative sources	Major dietary sources	Safety doses and route (Reference)	Colonic metabolites (Reference)
Polyphenol				
Quercetin ($C_{15}H_{10}O_7$) 	 Red onion	Onion, apple, broccoli, tea, honey, lemon, tomato and strawberry	Dose: 4 g Route: Oral Model: Human (Gugler et al., 1975)	Quercetin-3′-O-sulfate, quercetin-3-O-glucuronide, isorhamnetin-3-O-glucuronide (Mullen et al., 2006)
Anthocyanin ($C_{15}H_{11}O_6CI$) 	 Purple corn	Strawberry, blueberry, grapes, blackberry, blackcurrant, purple cauliflower and corn	Dose: 45 g/day (given as freeze-driedblack raspberries) Route: Oral Model: Human (Stoner et al., 2005)	3,4-Dihydroxybenzoic acid, 3-(3′-hudroxyphenyl)propionic acid, 4′-hydroxyphenylacetic acid, 4′-hydroxyhippuric acid, 4′-hydroxymandelic acid (González-Barrio et al., 2011)
Genistein ($C_{15}H_{10}O_5$) 	 Soybean	Soybean, yellow pea, green lentil, kudzu and lupine	Dose:150 mg/kg/day Route: Oral Model: Human (Kim, K.H. et al., 2013)	Dihydrogenistein, 6′-hydroxy-O-desmethylangolensin, 6′-hydroxy-O-desmethylangolensin (Coldham et al., 2002)
EGCG($C_{22}H_{18}O_{11}$) 	 Green tea	Green tea	Dose: 800 mg/day Route: Oral Model: Human (Chow et al., 2003)	5-(3′, 4′, 5′-Trihydroxyphenyl)-γ-valerolactone, 4′-hydroxyphenylacetic acid, 3′-methoxy-4′-hydroxyphenylacetic acid, 4′-hydroxybenzoic acid (Roowi et al., 2009)

Silibinin ($C_{25}H_{22}O_{10}$) 	 Milk thistle	Milk thistle (*Silybum marianum*)	Dose: 489 mg/ day (3 times) Route: Oral Model: Human (Hoh et al., 2007)	Silibinin diastereoisomers (Hoh et al., 2007)
kaempferol ($C_{15}H_{10}O_6$) 	 Grape	Apple, onion, citrus and grapes	Dose: 9 mg Route: Oral Model: Human (DuPont et al., 2004)	Kaempferol-3-*O*-glucuronide, kaempferol monosulfate (DuPont et al., 2004)
Caffeic acid ($C_9H_8O_4$) 	 Coffee	Coffee, olive oil, grains, and vegetables	Dose: 153.8 mg Route: Oral Model: Human (Wittemer et al., 2005)	4-ethylcatechol,3-(3-hydroxyphenyl)propionic acid (Aura, 2008)
Rosmarinic acid ($C_{18}H_{16}O_8$) 	 Rosemary	Rosemary, perilla and basil	Dose: 200 mg Route: Oral Model: Human (Baba et al., 2005)	Caffeic acid, 3(3,4-dihydroxyphenyl) lactic acid, ferulic acid, *m*-coumaric acid (Baba et al., 2005)
Ellagic acid ($C_{14}H_6O_8$) 	 Strawberry	Blackberry, raspberry and strawberry	Dose: 45 g/day (given as freeze-driedblack raspberries) Route: Oral Model: Human (Stoner et al., 2005)	Urolithins A and B (Seeram et al., 2006)

Gallic acid ($C_7H_6O_5$) 	 Walnut	Blueberry, walnut, apple, flax seed and green tea	Dose: 800 mg Route: Oral Model: Human (Roberts et al., 2007)	3-O-methylgallic acid, 4-O-methylgallic acid, 3,4-di-O-methylgallic acid (Hodgson et al., 2000)
Resveratrol ($C_{14}H_{12}O_3$) 	 Red grape	Red grape, berrie, plums and peanut	Dose: 5 g/day Route: Oral Model: Human (Patel et al., 2011)	Resveratrol-3-O-glucuronide, resveratrol-4′-O-glucuronide, resveratrol-3-O-sulfate, resveratrol-4′-O-sulfate, resveratrol-O-disulfate (Patel et al., 2010)
Curcumin ($C_{21}H_{20}O_6$) 	 Turmeric	Turmeric (*Curcuma longa*)	Dose: 12,000 mg/day Route: Oral Model: Human (Lao et al., 2006)	Curcumin glucuronide,curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin (Ireson et al., 2002)
Terpenoids				
Ursolic acid ($C_{30}H_{48}O_3$) 	 Apple	Rosemary, basil, apple, peppermint, oregano and sage	Dose: 98 mg Route:Intravenous Model: Human (Zhu, Z. et al., 2013)	Ursonic acid methyl ester, 3-oxoursa-1,12-dien-28-oic acid methyl este, 3-oxoursa-1,12-dien-28-oic acid, 3-oxoursa-1,12-dien-28-oic acid methyl este (Leipold et al., 2010)
Betulinic acid ($C_{30}H_{48}O_3$) 	 White birch	White birch	Dose: 500 mg/kg/day Route: Intraperitoneal Model: Mouse (Pisha et al., 1995)	

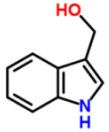
Organosulfur Compounds				
Sulforaphane ($C_6H_{11}NOS_2$) 	 Broccoli	Cruciferous vegetables	Dose: 150-200 µmol/ day Model: Human (Alumkal et al., 2015; Singh et al., 2014)	Sulforaphane–gluthatione, sulforaphane–cysteine, sulforaphane-*N*-acetylcystein (Dominguez-Perles et al., 2014)
Indole-3-carbinol (C_9H_9NO) 	 Cauliflower	Cruciferous vegetables	Dose: 400 mg/day Route: Oral Model: Human (Reed et al., 2005)	3,3'-diindolylmethane (Aggarwal and Ichikawa, 2005)

Table 2

Use of dietary phytochemicals for CRC prevention and their associated molecular targets: evidence in preclinical studies.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	Reference
Polyphenols				
Quercetin	-25-200 µM for 48 h, *In vitro*:HT-29	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis	-↓p-Akt, MYC -At G0/G1 phase -↓Bcl-2, ↑Bax, p53, caspase-3	(Yang et al., 2016)
	-10-100 µM for 24-48 h, *In vitro*:CT-26 -10 or 50 mg/ kg, *In vivo*: lung metastasis model of CRC	-Induces apoptosis -Suppresses metastasis -Decreases tumor nodules and lung weights	-↑c-PARP, caspase-3,-9, ↓Bcl-2, Bcl-xL -↑p-Erk, p-JNK, p-p38MAPK -↓MMP-2, MMP-9, N-cadherin, β-catenin, Snail, ↑E-cadherin	(Kee et al., 2016)
	-25-100 µM for 24 h, *In vitro*: Caco-2 and SW-620	-Induces apoptosis	-↑Bax, caspase-3,-9, ↓Bcl-2, NF-κB	(Zhang et al., 2015)
	-5-50 µM for 24-72 h, *In vitro*: DLD-1	-Induces apoptosis	-↓MMP	(Cincin et al., 2015)
	-25-100 µM for 6- 24h, *In vitro*: HCT-116	-Induces apoptosis	-↓MMP, ↑ROS -↑SIRT-2/p-AMPK/p-p38MAPK -↑SIRT-2/p-AMPK/↓p-mTOR	(Kim, G.T. et al., 2014) (Kim, G.T. et al., 2013)
	-50 µM for 48h, *In vitro*: Caco-2 and DLD-1	-Inhibits cell proliferation -Induces apoptosis	-↓CBI receptor, Wnt/β-catenin, p-GSK3β, p-PI3K/Akt, p-S6, p-4EBPI, p-STAT3 -↑JNK, c-Jun	(Refolo et al., 2015)
	-0.1 or 1 µM, *In vitro*: DLD-1	-Induces apoptosis	-↑caspase-3,c-PARP, p-p38MAPK	(Bulzomi et al., 2012)
	-25-100 µM for 24h, *In vitro*: HCT-116 -50 mg/kg for 24 days, *In vivo*: HCT-116 Xenograft model	-Induces apoptosis -Arrests cell cycle	-↓Hypoxia induces AMPK, HIF-1 -At G0/G1 phase	(Kim et al., 2012)
	-20-100 µM for 24h, *In vitro*: HT-29 and HCT-15	-Inhibits cell proliferation -Induces apoptosis	-↓p-Akt, p-GSK3β, Cyclin D1 -↑COX-2 dependent ROS -↑Caspase-3,cyto- c	(Raja et al., 2017)
	-10-120 µM for 48h, *In vitro*: CT-26 -50-200 mg/kg for 18 days, *In vivo*: CT-26 Xenograft model	-Induces apoptosis -Reduces tumor volume		(Hashemzaei et al., 2017)

	-5 µM, *In vitro*: Caco-2	-Decreases inflammation -Suppresses migration and invasion	-↓TLR4, NF-κB, TNF-α, COX-2 and IL-6 -↓MMP-2, MMP-9, ↑E-cadherin	(Han et al., 2016)
Isoquercitrin	-75-150 µM for 24h,*In vitro*: HCT-116, DLD-1 and SW-480 -150 µM, *In vivo*: *Xenopus*embryos	-Inhibits cell proliferation -Anti-tumor effects	-↓Wnt/β-catenin	(Amado et al., 2014)
Quercetin derivative	-25-50 µM for 24h, *In vitro*: HCT-116	-Induce oxidative stress -Induces ER stress -Induces apoptosis	-↑ROS -↑IRE1-α, XBP-1, Ca^{2+} ions -↓MMP, ↑p-JNK, Bax, cyto- c, caspase-3,-9, ↓Bcl-2	(Khan et al., 2016)
	-5-40 µM for 24h, *in vitro*: HT-29 and HCT-116 -500 µM for 24h, *in vivo*: *S.cerevisiae*strain RDKY3615	-Induces oxidative stress -Arrests cell cycle -Induces autophagy	-↑ROS - At G2/M phase -↑LC-I/II, ↓Beclin, SQSTM1/p62, p-Akt/PI3K, ↑p-Erk1/2, p-JNK, p-p38MAPK	(Enayat et al., 2016)
	-15 µM for 24h, *In vitro*: SW-620 and HCT-116	-Arrests cell cycle -Induces autophagy	-At G2/M phase -↑LC-I/II, ↓Beclin, SQSTM1/p62, ↑Atg7, p-Erk1/2, p-JNK, p-p38MAPK	(Zhao, Y. et al., 2017)
Anthocyanin	-5-45 µg/mL for 48h, *In vitro*: HCT-116	-Suppresses migration and invasion	-↓Claudin,↑p38MAPK, ↓PI3K/Akt, -↓MMP-2, MMP-9	(Shin et al., 2011)
	-0.5-25 µg/mL for 72h, *In vitro*: HCT-116, Caco-2 and SW-480	-Demethylates tumor suppressor genes	-↓DNMT1, DNMT3B, β-catenin, c-MYC, Wnt	(Wang, L.-S. et al., 2013)
Anthocyanin rich extract	-25-100 µg/mL for 24h, *In vitro*: Colo 320DM and HT-29	-Induces apoptosis -Arrests cell cycle	-↑c-PARP, caspase-3, Bax/Bcl-2 -At G0/G1 phase -↓Cyclin E, cyclin D, ↑p21, p27	(Hsu et al., 2012)
	-5 µg/mL for 24h, *In vitro*: CRC stem cells -20% w/w for 4wks, *In vivo*: AOM-induced colon cancer	-Inhibits cell proliferation -Induces apoptosis -Decreases tumor incidence	-↓Wnt/β-catenin, c-MYC, cyclin D1 -↑p53, Bax/Bcl-2, cyto-c	(Charepalli et al., 2015)
	-0.25-10 mg/mL for 24h, *In vitro*: HCT-116 and HT-29	-Induces apoptosis -Arrests cell cycle	-↓Survivin, cIAP-2 and XIAP -At G1 phase	(Mazewski et al., 2018)
	-1-20 µg/mL for 24h, *In vitro*: HT-29	-Inhibits cell proliferation -Decreases inflammation	-↑ROS -↓TNF-α, IL-1β, IL-6, and NF-κB	(Venancio et al., 2017)
	-1-10% for 9 wks, *In vivo*: AOM and DSS-induced Balb/c mice	-Suppresses inflammation -Reduces tumor growth and development		(Lippert et al., 2017)
	-50-500 µg/mL for 72h, *In vitro*: HT-29	-Induces epigenetic modification	-Suppresses DNA damage	(Esselen et al., 2011)

Anthocyanin metabolites	-100-150 µmol/L for 48h, *In vitro*: HT-29	-Induces apoptosis	-↑Caspase-3	(López de las Hazas et al., 2016)
	-50 µM for 24-48h,*In vitro*: Caco-2	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis	-↓NF-kB, AP-1, STAT-1, and OCT-1 -At G0/G1 phase -↑Caspase-3	(Forester et al., 2014)
Proanthocyanidins	-10-80 µg/mL for 48h, *In vitro*: SW-480 and SW-620	-Induces apoptosis	-↑Caspase-8, p-p38MAPK	(Minker et al., 2015)
	-25-200 µg/mL for 24h, *In vitro*: SW-620 -5-20 µg/egg for 5 days, *In vivo*: Xenografted chick chorioallantoic membrane model	-Suppresses angiogenesis	-↓VEGF, Ang1	(Huang et al., 2012)
Hexamericprocyanidins	-10 µM for 6h, *In vitro*: Caco-2	-Inhibits cell proliferation	-↓ERK, p38MAPK, Akt, and AP-1	(Da Silva et al., 2012)
Genistein	-10-50 µM for 12h, *In vitro*: HT-29	-Inhibits cell proliferation	-↓β-catenin	(Lepri et al., 2014)
	-5-45 mg/kg, *In vivo*: DMH-induced wistar rats	-Suppresses cancer progression	-↓PCNA, ↑Nrf2, HO-1, ↓β-catenin, stem cell marker	(Sekar et al., 2016)
	-140 mg/kg for 6 wks, *In vivo*: AOM-induced male Sprague-Dawley rats	-Suppresses pre-neoplasis	-↓Wnt/β-catenin, cyclin D1,c-Myc	(Zhang, Y. et al., 2013)
	-5-100 µM for 24h,*In vitro*: HCT-116	-Inhibits cell proliferation	-↓EGFR	(Gruca et al., 2014)
	-30-70 µM for 48h, *In vitro*: HT-29	-Inhibits cell proliferation -Induces apoptosis -Suppresses migration and invasion	-↓p-p38 MAPK -↑Caspase-3 -↓MMP-2	(Shafiee et al., 2016)
	-20-100 µM for 6h, *In vitro*: LoVo and HT-29	-Induces apoptosis	-↓NF-κB, Bcl-2, ↑Bax	(Luo et al., 2014)
	-0-100 µmole/L for 2h, *In vitro*: HCT-116	-Induces apoptosis -Arrests cell cycle	-↓MMP, ↑ROS -At G2/M phase	(Wu et al., 2017)
	-0.1-0.2 µM for 24h, *In vitro*: Caco-2	-Inhibits cell proliferation -Arrests cell cycle	-↓Cyclin B1, ChK2 -At G2/M phase	(Han et al., 2013)
	-10-100 µM for 48h, *In vitro*: HCT-116 and SW-480	-Induces apoptosis -Arrests cell cycle	-↓cdc2, cdc25A, ↑ATM/p53, p21waf1/cip1, GADD45α	(Zhang, Z. et al., 2013)
	-50-200 µM for 24h, *In vitro*: HCT-116	-Suppresses cell proliferation -Arrests cell cycle	-↓DNA topoisomerase II activity -At G2/M phase	(Mizushina et al., 2013)
	-10 µmole/L for 24-48h, *In vitro*: HCT-116,HT-29 and SW-620 -25-75 mg/kg/day for 5 wks, *In vivo*: Balb/c mice	-Suppresses metastasis	-↓MMP-2, FLT4, CD34.	(Xiao et al., 2015)
	-1-75 µmol/L for 48h, *In vitro*: SW-480	-Induces epigenetic modification	-↑DKK1	(Chiou et al., 2012)

	-10-200 µM for 24h, *In vitro*: HT-29	-Induces epigenetic modification	-↓HDAC1	(Groh et al., 2013)
Genistein derivative	-5-20 µM for12-24h, *In vitro*: HCT-116 and HT-29 -5-45 mg/kg, *In vivo*: AOM and DSS-induced C57BL/6 mice	-Decreases inflammation -Inhibits cell proliferation -Arrests cell cycle -Reduces mortality, tumor number and volume.	-↓NF-κB/p65,TNF-α, IL-6, IL-1β -At G0/G1 phase -↑APC, AXIN2,CDX2, ↓p-GSK3β, β-catenin, PCNA, cyclin D1, c-MYC	(Du et al., 2016)
	-1-100 µM for 24h, *In vitro*: HCT-116	-Inhibits cell proliferation -Arrests cell cycle -Decreases inflammation	-↓PCNA, Bcl-2, cyclin D1 -At G0/G1 phase -↓NF-κB, p-IκB, IKKα/β	(Wang, Y., 2016)
Epigallocatechin-3-gallate (EGCG)	-10 µM for 48h, *In vitro*: DLD-1	-Inhibits cell proliferation -Induces apoptosis	-↓PI3K/Akt -↑c-PARP, caspase-9	(Kumazaki et al., 2013)
	-40-80 µM for 48h, *In vitro*: SW-480	-Inhibits cell proliferation	-↓Wnt, cyclin D1, c-MYC	(Oh et al., 2014)
	-25-100 µM for 48h, *In vitro*: HCT-116 and HT-29	-Induces apoptosis -Suppresses migration and invasion	-↑p53 -↑AMPK, ↓MMP-2, VEGF	(Park et al., 2013)
	-1-50 µM for 1h, *In vitro*: HCT-116 and HT-29	-Induces apoptosis	-↑p-Erk1/2, p-JNK1/2, p-p38MAPK	(Cerezo-Guisado et al., 2015)
	-100 µg/mL for 15 min, *In vitro*: SW-480	-Inhibits cell proliferation -Suppresses migration	-↓Erk1/2, NF-κB -↑Caspase-7 -↓MMP-2, TF	(Zhou et al., 2012)
	-10 µg/mL for 4-24h, *In vitro*: LoVo and Caco-2	-Induces apoptosis -Arrests cell cycle	-↑Bax, ↓Bcl-2, ↑caspase-9, PARP, ROS -At G0/G1 phase	(Papi et al., 2013)
	-50-150 µM for 48-72h, *In vitro*: HT-29, HCT-116, SW-480 and SW-48	-Induces epigenetic modification	-↓RXRα, β-catenin, cyclin D1	(Morris et al., 2016)
	-50-150 µM for 48-72h, *In vitro*: HT-29 and HCT-116	-Controls DNA methylation	-↓DNMT3A, HDAC3	(Moseley et al., 2013)
EGCG+ sodium butyrate	-10 µM for 48h, *In vitro*: HT-29, RKO and HCT-116	-Induces apoptosis -Arrests cell cycle -Induces epigenetic modification	-↑p53, p21, ↓survivin -At G1 and G2/M phase -↑DNA damage, ↓DNMT1, ↑HDAC1, ↓CpG methylation	(Saldanha et al., 2014)
Peracetylated EGCG	-0.017-0.085% for 14 days, *In vivo*: DSS-induced colitis in ICR mice	-Decreases inflammation -Increases anti-oxidant enzyme -Induces epigenetic modification	-↓p-PI3K/Akt/ p-NFκB, p65 acetylation, iNOS, COX-2, TNF-α, IL-1β, IL-6 -↑HO-1, Nrf2, p-Erk1/2 -↓Acetylation of histone 3 lysine 9 (H3K9), p65/RelA	(Chiou et al., 2012)
Kaempferol	-60 µmol/L for 24h, *In vitro*: HT-29	-Inhibits cell proliferation -Induces apoptosis	-↓IGF-IR, ErbB3, p-PI3K/Akt, p-Erk/12	(Lee et al., 2014a)

	-60 µmol/L for 24-48h, *In vitro*: HT-29 and SW-480	-Induces apoptosis	-↑c-Caspase-3, -7, -9, PARP, Bik, Bad, ↓Bcl-xL -↑FasL, cyto-c	(Lee et al., 2014b)
	-20-60 µmol/L for 6h, *In vitro*: HT-29	-Arrests cell cycle	-At G1 and G2/M phase -↓CDK2, CDK4, Cdc25C, Cdc2, cyclin B1, cyclins D1, cyclin E, cyclin A, p-Rb	(Cho and Park, 2013)
	-50-200 mg/kg for 4 wks, *In vivo*: DMH induced male Wistar rats	-Prevents oxidative damage	-↓Lipid peroxidation, ↑CAT, SOD, GPx	(Nirmala and Ramanathan, 2011)
	5-100 µM for 10h, *In vitro*: HCT-116	-Induces epigenetic modification	-↑Hyperacetylation of histone complex H3	(Berger et al., 2013)
Silibinin	-300 µM for 24h, *In vitro*: SW-480 and SW-620	-Induces apoptosis	-↑DNA fragmentation -↑Caspase-3, -8, -9, -10, Bid, cyto-c, TRAIL, DR4/DR5 -↓Mcl-1, XIAP	(kauntz et al., 2012a)
	-50-100 µM for 24h, *In vitro*: p53 wild and null type HT-29	-Induces apoptosis	-↑NAG-1, EGR-1 -↑ROS, c-PARP	(Woo et al., 2014)
	-100 µM, *In vitro*: HT-29, SW-480 and LoVo	-Inhibits cell proliferation	-↓IL-4,IL-6, p-STAT3, NF-κB.	(Kumar et al., 2014)
	-10^{-5}–10^{-8} M for 4h, *In vitro*:LoVo	-Suppresses migration and invasion	-↓MMP-2, JNK, AP-1	(Lin et al., 2012)
	-5-50 µg/mL for 24-72h, *In vitro*: Cancer stem-like cells and HT-29 -5 µg/mL for 15 days, *In vivo*: Xenograft tumor model	-Suppresses CSC self regeneration and sphere formation -Reduces tumorigenecity and tumor growth	-↓AKTSer473/mTOR, PP2Ac	(Wang, J.Y. et al., 2012)
	-5 mg/Kg for 7 wks, *In vivo*: DSS-induced male Wistar rat	-Decreases tumor growth -Induces apoptosis -Suppresses inflammation	-↓ACF proliferation and formation -↓Bcl-2, ↑Bax -↓MMP-7, TNFα, IL1β	(Kauntz et al., 2012b)
	-0.2%,*In vivo*: Apc−/+ mice	-Decreases intestinal adenoma formation -Induces apoptosis -Suppresses cell cycle entry	-↓Cdk4, cyclin D1, p-Rb -↓Ki-67	(Karim et al., 2013)
	-50 mg/kg for 32 wks, *In vivo*: DMH induced rat	-Decreases adenoma formation	-↑CDX2	(Sangeetha and Nalini, 2015)
	-300 µM for 24h, *In vitro*: SW-480 and SW-620	-Induces epigenetic modification	-↓DNMT	(Kauntz et al., 2013)
Silybin and regorafenib	-90 µM for 72h, *In vitro*: SW-48, SW-48CR, HCT-15 and SW-480	-Inhibits cell proliferation -Induces apoptosis	-↓PI3K/Akt/mTOR -↑ROS	(Belli et al., 2017)
Silibinin+1,25-dihydroxyvitamin D	-1-100 µM for 24-72h, *In vitro*: HT-29	-Inhibits cell proliferation -Suppresses migration	-↓Snail1, snail2 -↑VDR	(Bhatia and Falzon, 2015)

Silibinin +Oxidovanadium (IV)	-25-100 µM for 24h, *In vitro*: HT-29	-Induces apoptosis	-↑Caspase-3, ↓NF-κB -↓Topoisomerase IB	(León et al., 2015)
Silibinin+metformin	-50-200 µmol/L for 24h, *In vitro*: COLO-205	-Inhibits cell proliferation -Induces apoptosis	-↓p-Akt, ↑PTEN, ↓p-mTOR, ↑AMPK -↑Caspase-3, AIF	(Tsai et al., 2015)
Silibinin +hydrogels	-100-800 mg/kg for 2 wks, *In vivo*: Xenografted CRC mice	-Suppresses angiogenesis	-↓VEGF	(Cho et al., 2012)
Gallic acid	-10-100 µM for 24-72h, *In vitro*: Caco-2	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis	-↓NF-kB, AP-1, STAT-1, OCT-1 -At G0/G1 phase -↓Cyclin D1 -↑Caspase-3	(Forester et al., 2014)
	-740 µmol/L for 24-72h, *In vitro*: HCT-15	-Induces apoptosis	-↑ROS, ↓MMP	(Subramanian et al., 2016)
	-40 µg/mL for 2-6 days, *In vitro*: HCT-116	-Inhibits cell proliferation	-↓CSC markers -↓Notch1, Wnt/β-catenin	(Lee et al., 2016)
	-25 mg for 8 wks, *In vivo*: DSS induced colitis in rat model	-Decreases inflammation	-↓iNOS, COX-2, IL-6 -↓p-STAT3Y705, p-IκB, p65-NF-κB	(Pandurangan et al., 2015)
Ellagic acid	-25-100 µg/mL for 48h, *In vitro*: Caco-2 and HCT-116	-Inhibits cell proliferation -Induces apoptosis -Arrests cell cycle	-↓PCNA, K-ras, p-PI3K/Akt -↑Caspase-8 -At G1 phase	(Yousef et al., 2016a; Yousef et al., 2016b)
	-20-60 µM for 24h, *In vitro*: HCT-15	-Inhibits cell proliferation -Induces apoptosis	-↓PCNA, cyclin D1, p-PI3K/Akt -↑ROS, Bax, Cyto-c, ↓Bcl-2, ↑caspase-3 -↑DNA fragmentation	(Umesalma et al., 2015)
	-60 mg/kg for 7 wks, *In vivo*: DMH induced male Wistar rats	-Anti-cancer effects	-↑Antioxidant status -↓ACF formation, c-MYC	(Kumar et al., 2012)
	-60 mg/kg for 15 wks, *In vivo*: DMH induced male Wistar rats	-Inhibits cell proliferation -Induces apoptosis -Suppresses angiogenesis -Decreases detoxification	-↓PCNA -↑P53 -↓MMP-2 and MMP-9 -↓Phase I and ↑phase II enzyme	(Umesalma et al., 2014)
	-25 mg for 8 wks, *In vivo*: DSS induced colitis in rat model	-Decreases inflammation	-COX-2, iNOS -↓p-p38MAPK, NF-κB, and p-STAT3	(Marín et al., 2013)
Ellagic acid derivatives or metabolites	-5-50 µM for 72h, *In vitro*: SW-620	-Inhibits cell proliferation	-↓Wnt	(de Molina et al., 2015)
	-5-30 µg/mL for 24-48h, *In vitro*: HT-29	-Induces apoptosis -Arrests cell cycle	-↑Caspase-3, -8, -9, c-PARP,↓MMP -At G1 and G2/M phase -↑p21	(Cho et al., 2015)

	-50-100 µM for 24- 48h, *In vitro*: HCT-116, Caco-2, SW-480	-Arrests cell cycle	-At S and G2/M phase	(González-Sarrías et al., 2014; González-Sarrías et al., 2017)
	-100 µM for 48h, *In vitro*: Caco-2, HT-29, and SW-480	-Modulates miR levels	-↑CDKN1A, miR-215, ↑miR-224	(González-Sarrías et al., 2016)
Ellagicacid + 5-FU	-2.5-25 µM for 24h, *In vitro*: HT-29	-Induces apoptosis	-↓MMP, ↑Bax/Bcl-2, caspase-3	(Kao et al., 2012)
Urolithin A+ 5-FU and 5'DFUR	-10-20 µM for 24h, *In vitro*: Caco-2, SW-480 and HT-29	-Induces apoptosis -Arrests cell cycle	-↑Caspase-8, -9 -At S and G2/M phase -↑Cyclin A, B1	(González-Sarrías et al., 2015)
Rosmarinic acid	-5-100 µM for 3-24h, *In vitro*: COLO-205	-Induces apoptosis	-↑Fas, FasL, caspase-3, -8, -9, Bid, Bax -↑Cyt-c, AIF, c-PARP, DFF-45	(Cheng et al., 2011)
	-2.5-10 mg for 16 wks, *In vivo*: DMH induced male Wistar rats	-Improves pre-malignant lesion and antioxidant status -Inhibits cell proliferation -Suppresses inflammation	-↓ACF formation, -↑Antioxidant status -↓PCNA -↓COX-2, TNF-α, IL-6, NFκB	(Karthikkumar et al., 2012; Karthikkumar et al., 2015)
	-2.5-10 mg for 16 wks, *In vivo*: DMH induced male Wistar rats	-Reduces tumor incidence and multiplicity -Induces apoptosis	-↓Polyp -↑Antioxidant status -↓phase I and ↑phase II enzyme -↑p53, caspase-3, -9, Bax, ↓Bcl-2	(Venkatachalam et al., 2013; Venkatachalam et al., 2016)
Caffeic acid	-500-2000 µM for 12-48h, *In vitro*: HCT-15	-Induces apoptosis -Arrests cell cycle	-↑ROS, ↓MMP -At sub-G1 phase	(Jaganathan, 2012)
	-2.5-40 µg/mL for 72h, *In vitro*: HCT-116	-Induces apoptosis	-↑c-PARP	(Yim et al., 2012)
	-70 µM for 24h, *In vitro*: HCT-116	-Controls DNA damage	-↓DNA topoisomerase II activity	(Kuriyama et al., 2013)
Caffeic acid derivatives	-10-100 µM for 24h, *In vitro*: HCT-116 and SW-480 -50 nmol/kg for 16 wks, *In vivo*: Xenograft model of CRC	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis -Anti-metastasis effects -Decreasestumor growth	-↓NF-κB, p-Akt, mTOR, Erk1/2, PCNA -↓FASN, ↑AMPK -At G0/G1 phase -↑p21, ↓cyclin D1, cyclin E, CDK4, c-MYC, Lamin A -↑E-cadherin, ↓N-cadherin -↑Survival rate	(Chiang et al., 2014)
	-10-80 µM for 48h, *In vitro*: HCT-116 and HT-29 -5-20 mg/kg for 42 days, *In vivo*: Xenograft model of CRC	-Induces apoptosis -Arrests cell cycle -Suppresses invasion -Decreasestumor growth	-↑p53, c-caspase-3, Bax, p38MAPK, cyto-c -At G0/G1 phase -↑p21, p27, ↓CDK4, c-MYC	(Tang et al., 2017)

			-↓VEFG -↑Survival rate	
Resveratrol	-1-10 µM for 14 days, *In vitro*: HCT-116 and SW-480	-Inhibits cell proliferation -Suppresses migration and invasion	-↓NF-κB, ↑Sirt1 -↓MMP-9, CXCR4	(Buhrmann et al., 2016)
	-1-100 µmol for 24-72h, *In vitro*: SW-620	-Inhibits cell proliferation -Induces apoptosis	-↓Ras, Raf, MEK, Erk1/2 -↑Bak1, Bok, Bik, Noxa, Bad, Bax, p53, Apaf1 -↓Bcl-2, Bcl-xL, Bag1 -↑c-caspase-3, -7, -9, PARP	(Chen et al., 2016)
	-20-80 µmol for 24-48h, *In vitro*: HCT-116 -5-150 mg/kg for 4 wks, *In vivo*: Xenograft model of CRC	-Inhibits cell proliferation -Suppresses tumor growth	-↓PI3K/Akt, Wnt/β-catenin	(Liu, Y.-Z. et al., 2014)
	-20-50 µM for ~~9~~20-22h, *In vitro*: HCT-116 and SW-480	-Inhibits cell proliferation	-↓Wnt/β-catenin, ~~GSK3β,~~ T brachyury, conductin, cyclin D1 -Disrupt TCF/ β-catenin interaction	(Chen et al., 2012)
	-10-100 µM for 24h, *In vitro*: HCT-116 and Caco-2	-Induces apoptosis -Arrests cell cycle	-↑c-PARP, caspase-7, -9 -At G1/S phase -↓Cyclin D1, CDK2, CDK4, PCNA, p21	(Liu, B. et al., 2014)
	-150-300 ppm for 91 days, *In vivo*: $APC^{CKO}/Kras^{mut}$ mouse model	-Suppresses tumor growth -Induces epigenetic modification	-↓K-ras, B-raf, Erk, PI3K/Akt, β-catenin -↑miR-96	(Saud et al., 2014)
	-20-40 µM for 24-48h, *In vitro*: LoVo -50-150 mg/kg for 4 wks, *In vivo*: Ectopic tumor model	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis -Decreases tumor growth	-↑PCNA, p38MAPK -At S phase -↑Bax, ↓Bcl-2	(Yuan et al., 2016)
	-10-50 µM for 48h, *In vitro*: Caco-2 and SW-480	-Anti-inflammatory effects	-↓iNOS, TLR-4, p-IκB, NF-κB	(Panaro et al., 2012)
	-10-30 µM for 72h, *In vitro*: HCA-17, SW-480 and HT-29	-Inhibits cell proliferation	-↓COX-2, PGE2	(Feng et al., 2016)
	-15-50 µM for 24-48h, *In vitro*: LoVo and HCT-116	-Suppresses invasion and metastasis	-↓Wnt/β-catenin, c-MYC, MMP-7	(Ji et al., 2013)
	-1-100 µM for 48h, *In vitro*: HT-29	-Induces epigenetic modification	-↑Histone gH2AX levels	(San Hipólito-Luengo et al., 2017)
Resveratrol analogue	-50 mg/kg for 8 wks, *In vivo*: AOM and DSS induced C57BL/6 mice	-Inhibits tumor growth -Suppresses inflammation	-↓NF-κB p65, TNF-α, IL-6, mouse mast cell protease-1	(Xuan et al., 2016)

	-1-10 µg/mL for 24h, *In vitro*: HCT-116 and HT-29	-Induces apoptosis	-↑TRAIL receptors, DR4, DR5, caspase-3, -8, -9, PARP -↑ROS, JNK	(Park et al., 2016)
	-25-100 µM for 24h, *In vitro*: HCT-116	-Inhibits cell proliferation -Induces apoptosis -Arrests cell cycle	-↓PI3K/Akt -↑Bax/Bcl-2 ratio, cyto-c, caspase-3, -8, -9, c-PARP -At G2/M phase	(Kim et al., 2017)
	-5-50 µM for 24h, *In vitro*: COLO-205 -10 mg/kg for 15 days, *In vivo*: Xenograft mouse model	-Inhibits cell proliferation -Induces apoptosis -Activates autophagy -Suppresses tumor growth	-↓p-mTOR/ p70S6K, PI3K/Akt, p-38MAPK, p-Erk1/2, p-JNK ½ -↑c-PARP, DFF-45, caspase-3, -8, -9 -↑LC3B I/II -↓COX-2, MMP-9, VEGF, cyclin D1	(Cheng et al., 2014)
Resveratrol metabolites	-30 µM for 48h, *In vitro*: SW-480 and SW-620	-Inhibits cell proliferation -Induces apoptosis -Arrests cell cycle	-↑γH2AX, ATR -↑p53, c-PARP, caspase-3 -At S phase -↑p21	(Aires et al., 2013)
	-1-100 µM for 48h, *In vitro*: Caco-2 and HCT-116	-Arrests cell cycle	-At G1 phase -↓Cyclin D1	(Polycarpou et al., 2013)
	-20-40 µM for 24-48h, *In vitro*: HCT-116 and HT-29	-Inhibits cell proliferation -Induces apoptosis -Arrests cell cycle	-↑p53, Bax, c-caspase-3, PARP -At S phase -↑p21, ↓cyclin E, p-Rb	(Sun et al., 2016)
Resveratrol + other polyphenols	-100 µM for 24h, *In vitro*: Caco-2	-Inhibits cell proliferation -Induces apoptosis	-↓p-Akt, MAPK/Erk1/2 -↑c-PARP, caspase-9	(De Maria et al., 2013)
	-9 µM for 24h, *In vitro*: CSC cells -0.03% and 0.12% w/w for 4 wks, *In vivo*: AOM induced tumor	-Inhibits cell proliferation -Induces apoptosis -Suppressestumor growth	-↓Wnt/β-catenin, c-MYC, cyclin D1 -↑p53, cyto-c, Bax/Bcl-2, c-PARP	(Reddivari et al., 2016)
	-0-30 µg/mL for 24h, *In vitro*: HT-29	-Induces epigenetic modification	-↓Sp1, Sp3, Sp4 -↓miR-27a, ZBTB10	(Del Follo-Martinez et al., 2013)
Resveratrol + 5-FU	-10 µM for 48h, *In vitro*: DLD-1	-Inhibits cell proliferation -Induces apoptosis -Induces epigenetic modification	-↓p-Akt, MAPK/Erk1/2 -↑p53, c-PARP -↑ miR-34a	(Kumazaki et al., 2013)
Curcumin	-15-45 mg/mL for 24-72h, *In vitro*: LoVo	-Inhibits cell proliferation -Induces apoptosis	-↓PI3K/Akt -↑Caspase-3, cyto-c, Bax, ↓Bcl-2	(Jiang et al., 2014)
	-30 µM for 4h, *In vitro*: HCT-116	-Inhibits cell proliferation -Induces autophagy	-↓EIF2, eIF4/p70S6K, p-mTOR -↑Autophagosome -↑Lamp1, Hsp70	(Wang, J. et al., 2016)

-200 µM for 1h, *In vitro*: SW-620 and SW-480	-Inhibits cell proliferation	-↓mTORC1, ↑p-Erk1/2, p-AMPKα1	(Sato et al., 2017)
-0.01-100 µM for 24h, *In vitro*: MC38	-Inhibits cell proliferation	-↓p-MEK	(Fenton and McCaskey, 2013)
-10-40 µmol/L for 24h, *In vitro*: SW-620	-Inhibits cell proliferation -Suppresses EMT	-↓Wnt, β-catenin, TCF4, ↑Axin -↑NKD2, E-cadherin, ↓vimentin, CXCR4	(Zhang, Z. et al., 2016)
-5-20 µM for 24h, *In vitro*: SW-480, HT-29 and Caco-2	-Decreases pro-protein convertase activity	-↓p-Akt	(Zhu, J. et al., 2013)
-20-25 µM for 24-48h, *In vitro*: HT-29 and DLD-1	-Induces apoptosis	-↑GRP78	(Chang et al., 2015)
-30-50 µM for 3-24h, *In vitro*: HCT-15	-Induces apoptosis	-↑ROS, ↓Prp4	(Shehzad et al., 2013)
-5-20 µM for 12-24h, *In vitro*: HCT-116	-Induces autophagy	-↑TFEB lysosomal pathway -↑LC3-II, ↓p62, Akt, mTOR	(Zhang, J., et al., 2016)
-10 µM for 24h, *In vitro*: SW-480 and LoVo	-Suppresses invasion	-↑AMPK, ↓p65 NF-κB, uPA, MMP-9	(Tong et al., 2016)
-0.1-0.25 mmol/kg for 7 days, *In vivo*: DSS induced tumor	-Decreases inflammation	-↓Cyclin D1, CDK4, p-STAT3	(Yang et al., 2013)
-0.02% with high protein diet for 8 wks, *In vivo*: AOM induced tumor	-Suppresses inflammation	-↓COX-2, iNOS, NO, TNF-α -↓Colonic proliferation	(Byun et al., 2015)
-300 mg/Kg/day for 7 wks, *In vivo*: AOM induced tumor	-Suppresses inflammation -Improves adipocytokine levels	-↓COX-2, TNF-α, IL-6, NF-κB, ↑AMPK -↓Leptin	(Kubota et al., 2012)
-1000-5000 ppm 16 wks, *In vivo*: DSS induced tumor	-Suppresses inflammation	-↓COX-2, iNOS	(Murakami et al., 2013)
-60 mg/kg/day for 12 wks, *In vivo*: DMH induced tumor	-Reduces oxidative and nitrosative stress -Reduces arginase activity -Induces apoptosis	-↓iNOS, ↑TGF-β1, HES-1 -↓ACF formation	(Bounaama et al., 2012)
-2.5-5 µM for 5 days, *In vitro*: HT-29	-Induces epigenetic modification	-↓CpG methylation -↓Histone deacetylases subtypes, DNA methyltransferases	(Guo et al., 2015)
-12.5 µM for 48h, *In vitro*: HCT-116	-Induces epigenetic modification	-↑miR-491, ↓PEG10, Wnt/β-catenin	(Li et al., 2018)
-10-30 µM for 24h, *In vitro*: RKO and SW-480	-Induces epigenetic modification	-↓miR-20a, miR-27a, miR-17-5p	(Gandhy et al., 2012)
-2.5-10 µg/mL, *In vitro*: SW-480 and HT-29	-Decreases drug resistance by inducing epigenetic modification	-Disrupt miR-27a-ZBTB1-SP	(Noratto et al., 2013)

Curcumin analogue	-0.01-100 µM for 24h, *In vitro*: MC38	-Inhibits cell proliferation -Induces apoptosis -Arrests cell cycle	-↓EGFR -↑Caspase-3, c-PARP, Bax/Bcl-2, ↓HSP90, HSP70 -At G2/M phase -↑p21, ↓cyclin D1, cyclin E, p-Rb	(Qiu et al., 2013)
	-5-60 µM for 48h, *In vitro*: SW-480	-Inhibits cell proliferation -Arrests cell cycle -Induces apoptosis	-↓GSK-3β -At G0/G1 phase, ↓cyclin D1 -↑Caspase 3, -8, -9	(Sufi et al., 2017)
	-10-20 µM for 6-24h, *In vitro*: HCT-116	-Inhibits cell proliferation -Induces apoptosis	-↓TNF-α induces NF-κB activation -↑Caspase-3, cyto-c, c-PARP -↑ROS, JNK, ↓MMP	(Waghela et al., 2015)
	-3.75 $X10^{-5}$ M for 24h, *In vitro*: HCT-116	-Activates nuclear receptor	-↑VDR, RAR, RXR	(Batie et al., 2013)
	-2.5-7.5 µM for 24h, *In vitro*: HCT-116, SW-480 and HT-29	-Induces apoptosis	-↑ROS, ↓MMP -↑Caspase-3, -9, cyto-c	(He et al., 2016)
	-2.5-10 µM for 24h, *In vitro*: HCT-116, SW-620 and CT-26 -25-50 mg/kg for 10-15 days, *In vivo*: Xenograft mouse model	-Induces apoptosis -Arrests cell cycle -Induces ER stress -Suppresses tumor growth	-↑ROS, c-PARP, c-caspase-3, ↓Bcl-2 -At G2/M phase -↓MDM2, CDC2, cyclin B1 -↑PKR, PERK, eIF2α, ATF4, CHOP	(Zhang et al., 2017)
	-20-30 µM for 24-48h, *In vitro*: HCT-116	-Induces apoptosis -Induces ER stress -Induces autophagy	-↑Caspase-7, -8, -9, cyto-c -↑CHOP, ATF6, XBP1, GRP78, HERPUD1 -↑Autophagosome formation, LC3-I to LC3-II conversion	(Basile et al., 2013)
	-3-9 µM for 24h, *In vitro*: SW-480	-Suppresses metastasis	-↓Zeb 1, Hef 1, Claudin 1	(Esmatabadi et al., 2015)
	-620nM-25µM for 24h, *In vitro*: HCT-116 and HT-29 -5-25 mg/kg for 3 wks, *In vivo*: Xenograft mouse model	-Decreases angiogenesis	-↓VEGF, HIF-1α, STAT-3, COX-2	(Rajitha et al., 2017)
	-100 nM for 72h, *In vitro*: HCT-116 and HT-29	-Induces epigenetic modification	-↓miR-21	(Roy et al., 2013)
	-2.0 µM for 48h, *In vitro*: HCT-116 and HT-29	-Increases therapeutic efficacy by inducing epigenetic modification	-↓miR-21	(Yu et al., 2013)
	-100 nM for 72h, *In vitro*: HCT-116	-Induces epigenetic modification	-↑miR-34a, miR-34c, ↓Notch-1	(Kubota et al., 2012)

	-5-20 µM for 12-48h, *In vitro*: DLD1, HCT116, LS513, and RKO	-Induces epigenetic modification	-↑Aryl hydrocarbon receptor activity	(Megna et al., 2017)
	-3-9 µM for 48h, *In vitro*: SW-480	-Suppresses drug resistance activity	-↓α, β integrin, ↑PDK4	(Javadi et al., 2017)
Curcumin + other compounds	-12.5 µM for 48h, *In vitro*: DLD-1	-Induces apoptosis	-↑Caspase-3, -7	(Montgomery et al., 2016)
	-25 ppm for 24h, *In vitro*: SW-480	-Induces apoptosis	-↑Caspase-3, Bax/Bcl-2	(Murthy et al., 2013)
	-7.5 µM for 24h, *In vitro*: HCT-116 and HT-29	-Inhibits cell proliferation -Induces apoptosis	-↓Sp1, Survivin, NF-κB -↑Caspase-3, -7, c-PARP, ROS, ↓MMP	(Sankpal et al., 2016)
	-0.0005-10 µg/mL for 24h, *In vitro*: HCT-116 -30 mg/kg for 10 days, *In vivo*: Xenograft mouse model	-Induces apoptosis	-↑DR4, DR5	(Yang et al., 2017)
	-0.2 wt %, *In vivo*: AOM induced tumor	-Suppresses inflammation -Decreases colon carcinogenesis	-↓IL-6, IL-1β, Akt, NF-κB	(Wu et al., 2017)
Curcumin + 5-FU	-5 µM for 24h, *In vitro*: HCT-116	-Suppresses metastasis ability	-↓NF-κB, TGF-β, p-Smad2	(Buhrmann et al., 2014)
	-30-130 µmol/L for 48h, *In vitro*: SW-480 and SW-620	-Induces apoptosis -Arrests cell cycle -Enhances ER stress	-↑Bax, cyto-c, ↓Bcl-2 -At G0/G1 phase -↑ROS, CHOP, Noxa	(Zhao, H. et al., 2017)
	-5 µM for 24h, *In vitro*: HCT-116 and HCT-116+ch3	-Inhibits cell proliferation -Induces apoptosis -Suppresses metastasis	-↓Cyclin D1, NF-κB, IκBα, PI3K, Src -↑Caspase-8, -9, -3, PARP, Bax , ↓Bcl-xL -↓MMP-9, CXCR4	(Shakibaei et al., 2015; Shakibaei et al., 2013)
Curcumin + diclofenac	-25-75 mg/kg for 6 wks, *In vivo*: DMH induced tumor	-Suppresses tumor growth -Induces apoptosis -Decreases telomerase activity -Arrests cell cycle	-↓PI3K/, Akt, PTEN -↑Bad, Bax, ↓Bcl-2, ↑caspase-3, -9 -↓TERT -↓CDK2, CDK4, cyclin D1, cyclin E -↑P53, Rb, p21	(Rana et al., 2015a; Rana et al., 2015b)
Terpenoids				
Ursolic acid	-20-80 µM for 24h, *In vitro*: HT-29 -12.5 mg/kg for 16 days, *In vivo*: Xenograft mouse model	-Inhibits cell proliferation -Suppresses angiogenesis -Decreases tumor volume	-↓SHH, p-STAT3,p-Akt, p-p70S6K -↓VEGF-A, bFGF	(Lin et al., 2013a)
	-20-80 µM for 24h, *In vitro*: HT-29	-Inhibits cell proliferation -Induces apoptosis	-↓PCNA, p-STAT3, p-Erk, p-JNK, p-p38MAPK	(Lin et al., 2013b)

	-12.5 mg/kg for 16 days, *In vivo*: Xenograft mouse model	-Arrests cell cycle -Reduces tumor growth	-↑Bax/Bcl-2 -AT G1/S phase, -↓Cyclin D1, CDK4, ↑p21	
	-20-60 µM for 48h, *In vitro*: HCT-15 and DLD-1	-Inhibits cell proliferation	↓β-catenin, cyclin D1, c-MYC, axin2	(Kim, J.-H. et al., 2014)
	-15 µM for 24h, *In vitro*: CT-29	-Induces apoptosis	-↑Caspase-3, c-PARP, Bax, ↓Bcl-2, survivin	(Koh et al., 2012)
	-10-20 µM for 48h, *In vitro*: SW-480 and LoVo	-Inhibits cell proliferation -Induces apoptosis -Suppresses migration	-↓p-PI3K/Akt, p-Erk, p-mTOR, COX-2, PGE-2, NF-κB -↑c-PARP, caspase-3, -9, cyto-c -↓MMP-9, ↑CDH1	(Wang, J. et al., 2013b)
Ursolic acid + capecitabine	-5-20 µM for 24h, *In vitro*: HCT-116 -250 mg/kg for 4 wks, *In vivo*: Xenograft mouse model	-Inhibits cell proliferation -Suppresses inflammation -Induces apoptosis -Suppresses metastasis -Increases chemo-sensitization -Decreases tumor volume	-↓Ki-67, STAT3, EGFR, β-catenin -↑p53, p21 -↓Bcl-xL, Bcl-2, cFLIP, survivin, cyclin D1 -↓COX-2, PGE2, NF-κB -↓MMP-9, BEGF, ICAM-1	(Prasad et al., 2012)
Ursolic acid + melatonin	-10-60 µM for 48h, *In vitro*: SW-480 and LoVo	-Inhibits cell proliferation -Induces apoptosis -Suppresses migration -Increases chemo-sensitization	-↓COX-2, NF-κB -↑Cyto-c, c-PARP, c-caspase-3, -9 -↓MMP-9	(Wang, J. et al., 2013a)
Ursolic acid + 5-FU and oxaliplatin	-20-40 µmol/L for 24h, *In vitro*: RKO, SW-480 and LoVo	-Reduces drug resistance activity -Suppresses angiogenesis -Increases chemo-sensitization	-↓MDR1 -↓HIF-1α, VEGF	(Shan et al., 2016)
Betulinic acid or its derivatives	-5-15 µM for 24-48h, *In vitro*: SW-480 and RKO 25 mg/kg for 22 days, *In vivo*: Xenograft mouse model	-Induces epigenetic modification -Decreases tumor growth	-↓Sp1, Sp3, Sp4 -↓Survivin, VEGF, p65-NFκB, EGFR, cyclin D1, pituitary tumor transforming gene-1 -↑ROS, miR-27a, ZBTB10	(Chintharlapalli et al., 2011)
	-14.9 µM for 12-48h, *In vitro*: HT-29	-Induces apoptosis	-↑ROS, DNA fragmentation, ↓MMP -↑Caspase-3, -9, Bax, Bad, ↓Bcl-2, Bcl-xl	(Chakraborty et al., 2015)
	-14.9 µM for 12-48h, *In vitro*: HT-29	-Induces autophagy	-↑Beclin1, Atg 3, Atg5, Atg 7, Atg 5-12 -↓p62, ↑LC3B, Bax -↓Proteasomal degradation	(Dutta et al., 2016)

Organosulfur Compounds				
Sulforaphene	-2.5-5 µM for 24h, *In vitro*: HCT-116 -1-5 mg/kg for 13 days, *In vivo*: Xenograft mouse model	-Induces apoptosis -Arrests cell cycle -Reduces microtubules polymerization -Decreases tumor growth	-↑c-PARP, p-MK2, p-p38MAPK, p-JNK -At G2/M phase, -↑ROS, ↓glutathione	(Byun et al., 2016)
	-25-100 µM for 24h, *In vitro*: Caco-2	-Regulates Phase II enzyme -Induces apoptosis -Arrests cell cycle	-↑UGT1A, Nrf2 -↑Bax, ↓Bcl-2 -At G1/G2	(Wang et al., 2014)
	-10-20 µM for 24h, *In vitro*: DLD-1, HCT-116 and LoVo	-Inhibits cell proliferation	-↑p27KIPI, ↓SKP2	(Chung et al., 2015)
	-10-40 µM for 48h, *In vitro*: HCT-116	-Induces apoptosis -Induces ER stress -Arrests cell cycle	-↑ROS, Ca^{2+}, ↓MMP, ↑cyto-c, DR4,DR5, TRAIL, caspase-3, -4, -8, -9, c-PARP -↑Calpain 1, ATF6α, ATF6β, GADD153, GRP78 -At G2/M phase -↑Cyclin A, cyclin B, CDK2, WEE1, ↓CDC25C, CDK1	(Liu et al., 2016)
	-25 µM for 24h, *In vitro*: Caco-2	-Induces autophagy	-↑LC3-II, UGT1A -↑Nrf2, hPXR	(Wang, M., 2012)
	-100 µg/mL for 72h, *In vitro*: Caco-2	-Improves drug delivery system	-↓EGFR degradation	(Behray et al., 2016)
	-5-20 µM, *In vitro*: SW-480	-Induces apoptosis	-↑ROS, ↓MMP, ↓Bcl2, ↑Bax, caspase-3, -7, -9 -↑p-Erk1/2, p-p38MAPK	(Lan et al., 2017)
	-12.5-50 µM for 6 h, *In vitro*: HCT-116	-Suppresses angiogenesis and migration	-↓HIF-1α, VEGF	(Kim et al., 2015)
	-*In vitro*: HCT-116 and RKO	-Induces epigenetic modification	-↓miR-21, HDAC1 -↓hTERT mRNA, telomerase protein, enzymatic levels	(Martin et al., 2018)
	-*In vitro*: HCT-116 and HT-29	-Induces epigenetic modification	-Controls pseudogene, *NMRAL2P*, *NQO1* induction	(Johnson et al., 2017)
Indole-3-carbinol derivatives	-0.5-4 µM for 24h, *In vitro*: HCT-116 and HT-29 -20-100 mg/kg for 21 days, *In vivo*: Xenograft mouse model	-Inhibits cell proliferation -Induces apoptosis -Decreases tumor growth	-↓Akt, mTOR, GSK3β -↑p53, p21, ↓Bcl-2, ASK1	(Kim et al., 2011)

-60 µM for 24-72h, *In vitro*: HCT-116 and Colo-320	-Induces apoptosis	-↑NDRG1	(Lerner et al., 2011)
-50 µM for 24h, *In vitro*: HCT-116 and SW-480	-Suppresses cell growth	-↓Cyclin D1, cyclin A, NF-κB	(Fadlalla et al., 2015)
-500 µM for 24h, *In vitro*: DLD1, HCT116, HT-29, LS513 and RKO	-Induces epigenetic modification	-↑Aryl hydrocarbon receptor activity, CYP1A1 mRNA expression	(Megna et al., 2016)

Table 3

Use of dietary phytochemicals for CRC prevention and their associated molecular targets: evidence in clinical studies.

Phytochemicals	Study subject	Dose and duration	Main outcome	Reference
Curcumin	Patients with ACF (n=41)	2-4 g/ day for 30 days	-↓ACF number (40%)	(Carroll et al., 2011)
	Patients with detected CRC (n=126)	360 mg three times/ day for 10 to 30 days	-↑P53, Bax, ↓Bcl-2	(He et al., 2011)
	Patients with advanced CRC (n=40)	3 g/ day for 1 month	-↑T helper 1 cells	(Xu et al., 2017)
Curcuminoids	Patients with detected CRC (n=15)	0.45, 0.9, 1.8 and 3.6 g/ day until disease progression or withdrawal	-↓PGE2 production in the blood	(Sharma et al., 2004)
	Patients with detected CRC (n=12)	0.45, 1.8, or 3.6 g/day for 1week before surgical procedure	-↓DNA oxidation	(Garcea et al., 2005)
Curcumin + quercetin	Patients with prior colectomy and FAP (n=5)	1.44 g curcumin and 60 mg quercetin /day for 6 months	-↓Number and size of adenomatous polyp	(Cruz–Correa et al., 2006)
Curcumin + silibinin	Patients with multiple adenomatous polyps	treatment for 3 months	-↓Colon polyp	(Alfonso-Moreno et al., 2017)
Resveratrol	Patients with resectable CRC (n= 20)	0.5 or 1 g/ day for 5 days	-↓Proliferation marker Ki-67 (5%)	(Patel et al., 2010)
Micronized resveratrol	Patients with hepatic metastasis CRC (n= 9)	5 g/ day for 10 to 21 days	-↑cleavedcaspase-3 (39%).	(Howells et al., 2011)
Grape powder and resveratrol	Patients with CRC (n= 8)	80 g grape powder with 0.07 mg resveratrol or 120 g grape powder with 0.11 mg resveratrol/ day for 19 days	-No significant changes were observed	(Nguyen et al., 2009)
Green tea extract	Patients with highly risk CRC (n= 163)	1.5 g/ day for 12 months	-↓Incidence of metachronouscolorectral adenomas and the size of relapsed adenomas	(Shimizu et al., 2008)
	Patients with metachronous colorectal adenoma (n=143)	0.9 g/ day for 12 months	-↓Recurrent polyps and relapsed adenomas	(Shin et al., 2017)
EGCG + apigenin	Patients with CRC (n= 36) and following polypectomy (n= 51)	20 mg EGCG and 20 mg apigenin/ day for 2-5 years	-↓The rate of colon neoplasia	(Hoensch et al., 2008)
EGCG with other polyphenols	Patients with hepatic metastasis CRC (n= 19)	237 or 474 mg/ day for 6-9 months	-↓Hepatic arterial infusion	(Baba et al., 2012)

Bilberry anthocyanins extract	Patients with CRC (n= 15)	1.4, 2.8 or 5.6 g/ day for 7 days	-↓Proliferation marker ki-67 (7%)	(Thomasset et al., 2009)
Silybin + regorafenib	Patients with metastatic CRC (n=22)	188 mg of silybin, 388 mg of phosphatidylcholine, and 60 mg of vitamin E/ day	-↑Survival rate of the patients	(Belli et al., 2017)
Pomegranate extract	Patients with CRC (n= 52)	900 mg/ day for 30 days	-Metabolites were detected in plasma, urine and colon tissue	(Nuñez-Sánchez et al., 2014)
Ellagetenins-containing pomegranate extract	Patients with CRC (n= 35)	900 mg/ day for 35 days	-↓CTNNB1, CDKN1A, CD44, TYMs and EGFR	(Nuñez-Sánchez et al., 2017)
Flavonoids (quercetin and rutin)	Patients with newly detected CRC	500 µM (quercetin + rutin)	-↓Oxidative stress	(Kurzawa-Zegota et al., 2012)

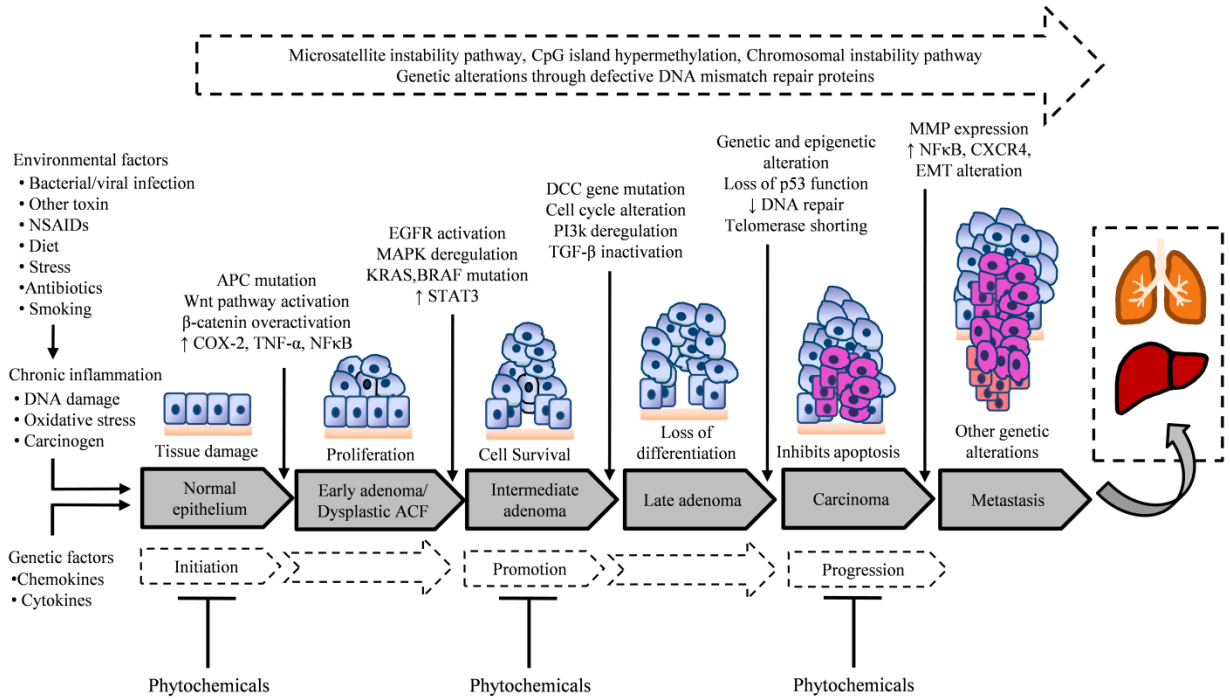
Table 4
Ongoing and completed clinical trials dealing with dietary phytochemicals as a single agent or as adjuvant in standard chemotherapies in CRC patients (https://clinicaltrials.gov).

Compound	Trial title	Phase	Intervention	Primary Purpose	Status	ClinicalTrials.gov Identifier
Curcumin	Curcumin in combination with 5-FU for CC	Phase 0	Drug: Curcumin and 5-FU	Treatment	Recruiting	NCT02724202
	Study investigating the ability of plant exosomes to deliver curcumin to normal and colon cancer tissue	Phase	DS: Curcumin and curcumin conjugated with plant exosomes	Treatment	Active, not recruiting	NCT01294072
	Phase III trial of gemcitabine, curcumin and celebrex in patients with metastatic CC	Phase 3	Drug: Celecoxib and Curcumin	Treatment	Unknown	NCT00295035
	Curcumin for the prevention of CC	Phase 1	DS: Curcumin	Prevention	Completed	NCT00027495
	Sulindac and plant compounds in preventing CC	-	DS: Curcumin and rutin Drug: Quercetin and sulindac	Prevention	Terminated	NCT00003365
	Curcumin in preventing CRC in patients undergoing colorectal endoscopy or colorectal surgery	Phase 1	DS :Curcumin Procedure: Diagnostic endoscopic and therapeutic conventional surgery	Prevention	Unknown	NCT00973869
	Combining curcumin with FOLFOX chemotherapy in patients with inoperable CRC	Phase 1and Phase 2	Drug: Oral complex C3 curcumin + chemotherapy and chemotherapy only	Treatment	Active, not recruiting	NCT01490996
	A prospective evaluation of the effect of curcumin on dose limiting toxicity and pharmacokinetics of irinotecan in patients with solid tumors	Phase 1	DS: Curcumin Drug: Irinotecan	Basic science	Active, not recruiting	NCT01859858
	Curcumin with pre-operative capecitabine and radiation therapy followed by surgery for rectal cancer	Phase 2	Drug: Curcumin and capecitabine Drug: Placebo Radiation: Radiotherapy	Treatment	Active, not recruiting	NCT00745134
	The effects of curcuminoids on ACF in the human colon	-	Drug: Sulindacand curcumin	Prevention	Terminated	NCT00176618
	Curcumin for the chemoprevention of CRC	Phase 2	Drug: Curcuminoids	Prevention	Completed	NCT00118989
	Use of curcumin for treatment of intestinal adenomas in FAP	-	Drug: Calcumin (Curcumin) Other: Risk factor, questionnaire,blood samples, biopsies (sigmoidoscopy and upper endoscopy)	Treatment	Recruiting	NCT00927485
	Avastin/FOLFIRI in combination With curcumin in CRC patients with unresectable metastasis	Phase 2	Drug: Avastin/FOLFIRI DS: Curcumin	Treatment	Enrolling by invitation	NCT02439385
	Curcumin biomarkers	Phase 1	Drug: Curcumin C3 tablet		Completed	NCT01333917
	Curcumin in treating patients with FAP	Phase 2	Drug: Curcumin Other: Laboratory biomarker analysis, placebo	Treatment	Active, not recruiting	NCT00641147

Resveratrol	Resveratrol for patients with CC	Phase 1	Drug: Resveratrol	Treatment	Completed	NCT00256334
	Phase I biomarker study of dietary grape-derived low dose resveratrol for CC prevention	Phase 1	DS: Grapes	Prevention	Unknown	NCT00578396
	Resveratrol in treating patients with CRC that can be removed by surgery	Phase 1	Drug: Resveratrol Other: pharmacological study and laboratory biomarker analysis	Treatment	Completed	NCT00433576
	A clinical study to assess the safety, pharmacokinetics, and pharmacodynamics of SRT501 in subjects with CRC and hepatic metastases	Phase 1	Drug: Placebo and SRT501	Basic Science	Completed	NCT00920803
Quercetin	Cancer associated thrombosis and isoquercetin (CAT IQ)	Phase 2 and Phase 3	Drug: Isoquercetin	Treatment	Recruiting	NCT02195232
Anthocyanin	Anthocyanin extract and phospholipid curcumin in colorectal adenoma	Phase 2	DS: Mirtoselect® + Meriva®	Prevention	Recruiting	NCT01948661
Genistein	Genistein in treatment of metastatic CRC	Phase 1 and Phase 2	Drug: Genistein	Treatment	Recruiting	NCT01985763
EGCG	Chemopreventive effects of EGCG in CRC patients	-	DS: EGCG	Prevention	Not yet recruiting	NCT02891538
	Oral GET and milk thistle extract to CRC patients undergoing resection	Phase 1	Drug: Green tea and milk thistle supplements	Treatment	Recruiting	NCT01239095
	Polyphenon E in treating patients with high-risk of CRC	Phase 2	Drug: Defined EGCG extractOther: Placebo,questionnaire administration and laboratory biomarker analysis	Treatment	Active, not recruiting	NCT01606124
	Minimizing the risk of metachronous adenomas of the colorectum with GET -MIRACLE-	Phase 2	DS: GET of *Camellia sinensis* DS: GET of *Camellia sinensis* followed by placebo	Prevention	Recruiting	NCT01360320
	GETs for the Prevention of colorectal Adenomas and CRC	-	DS: GTE	Prevention	Completed	NCT02321969
	Pilot study of GTE (Polyphenon E®) in ulcerative colitis	Phase 2	Drug: Polyphenon E®	Treatment	Completed	NCT00718094
Ellagitannins and ellagic acid	Pomegranate extract supplementation in CRC patients	Phase 1 and Phase 2	DS: Standard pomegranate extract formulation DS: Pomegranate extract formulation-1 and -2	Treatment	Completed	NCT01916239

Colon cancer, CC; Colorectal cancer, CRC; Fluorouracil, 5-FU; Dietary Supplement, DS; Aberrant crypt foci, ACF; Familial adenomat polyposis, FAP; Epigallocatechin gallate, EGCG; Green tea extract, GTE.

Fig. 1.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• Smoking
Chronic inflammation
• DNA damage
• Oxidative stress
• Carcinogen
Genetic factors
•Chemokines
• Cytokines
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Wnt pathway activation
β-catenin overactivation
↑ COX-2, TNF-α, NFκB
EGFR activation
MAPK deregulation
KRAS,BRAF mutation
↑ STAT3
DCC gene mutation
Cell cycle alteration
PI3k deregulation
TGF-β inactivation
Genetic and epigenetic alteration
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↓ DNA repair
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EMT alteration
Tissue damage
Proliferation
Cell Survival
Loss of differentiation
Inhibits apoptosis
Other genetic alterations
Normal epithelium
Early adenoma/ Dysplastic ACF
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Progression
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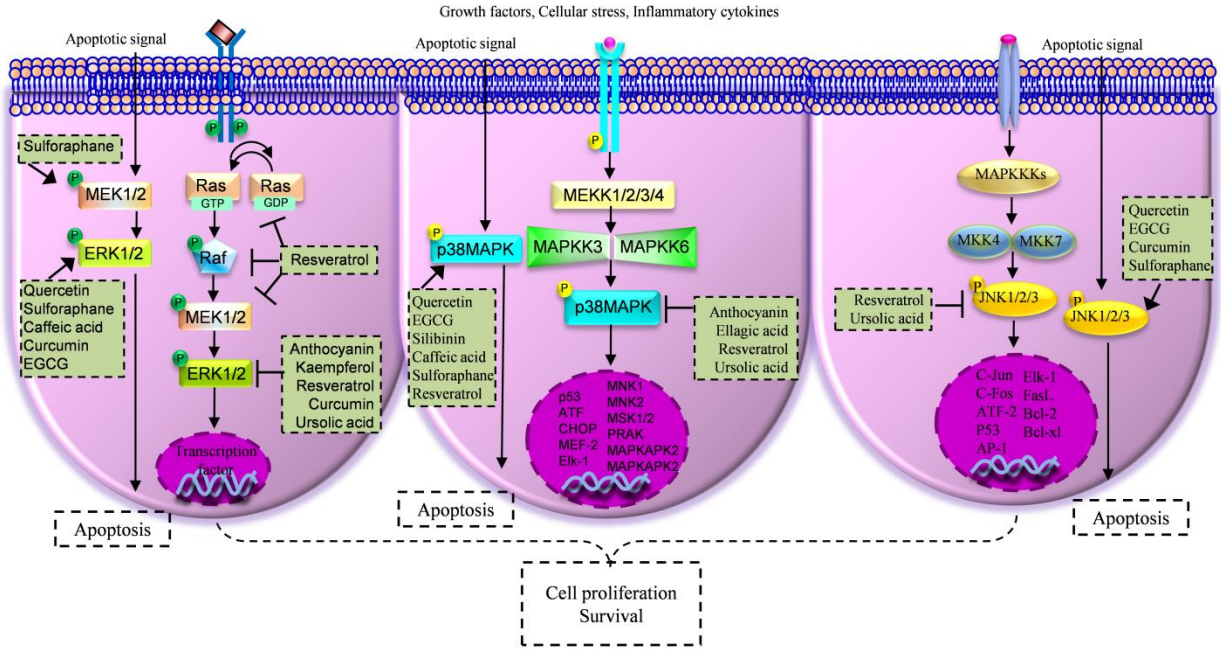
Phytochemicals
Phytochemicals

Fig. 2.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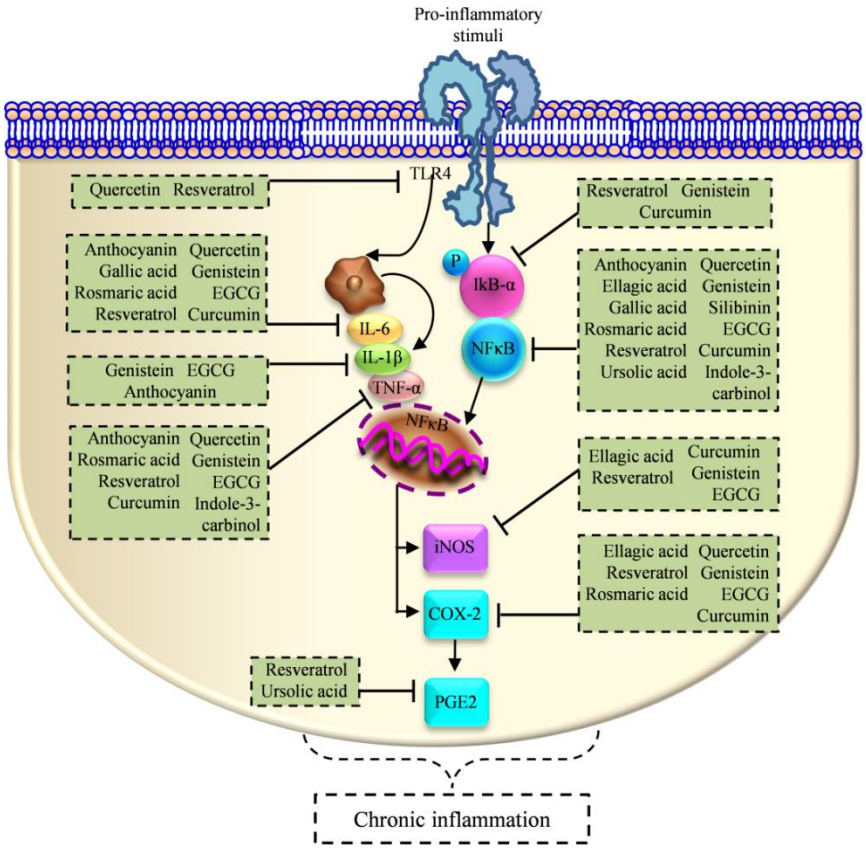
Cell proliferation
Survival

Fig. 3.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NFκB
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PGE2
Chronic inflammation

Fig. 4.

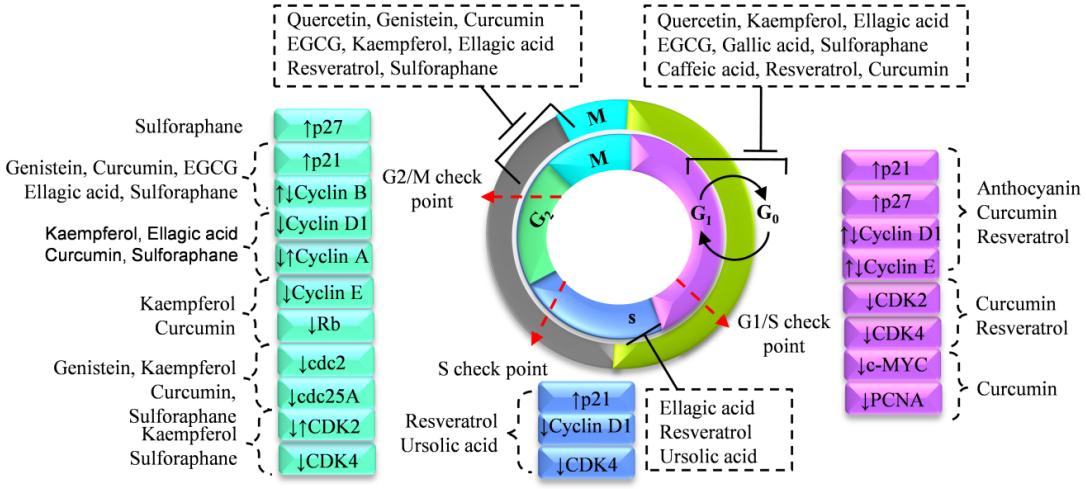
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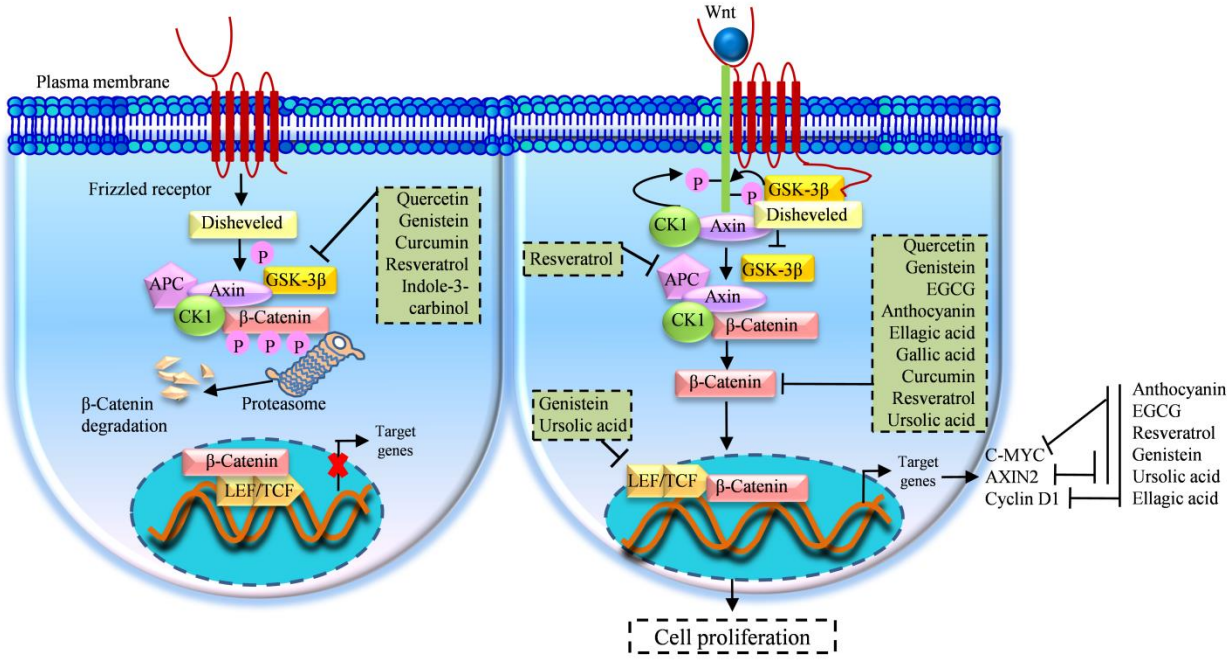
Fig. 5.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Ursolic acid
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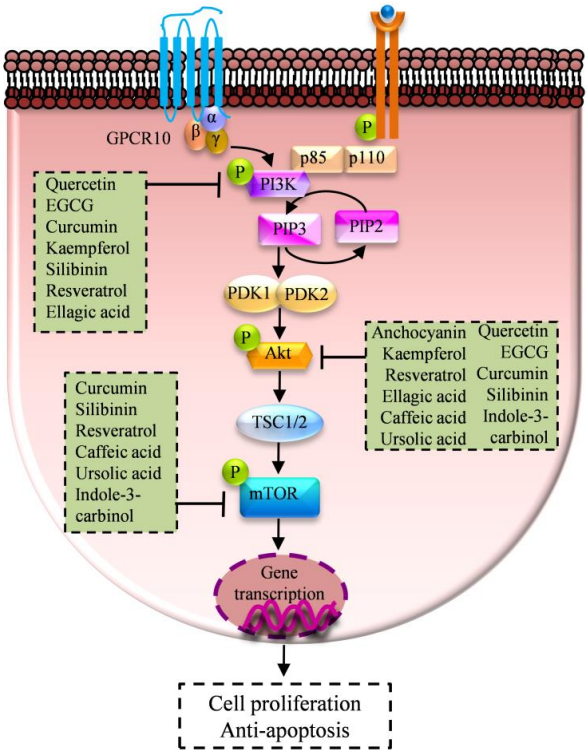
Cell proliferation

Fig. 6.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P
mTOR
Gene transcription
Cell proliferation
Anti-apoptosis
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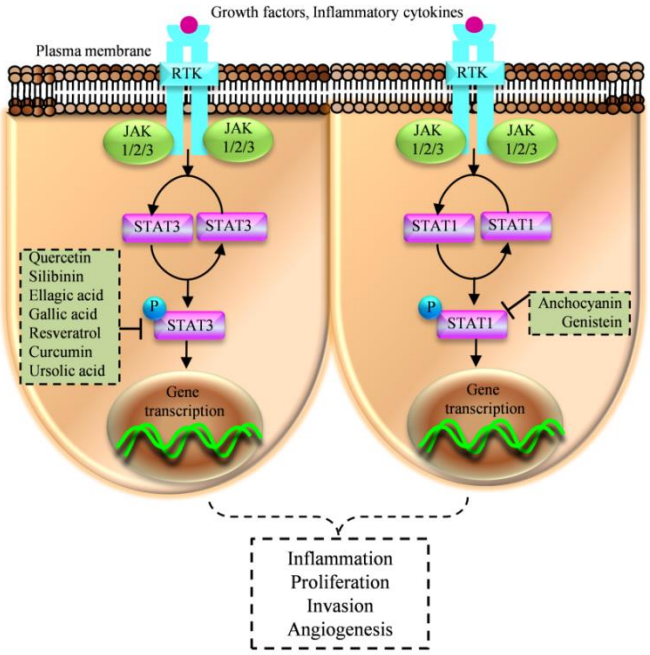
Fig. 7.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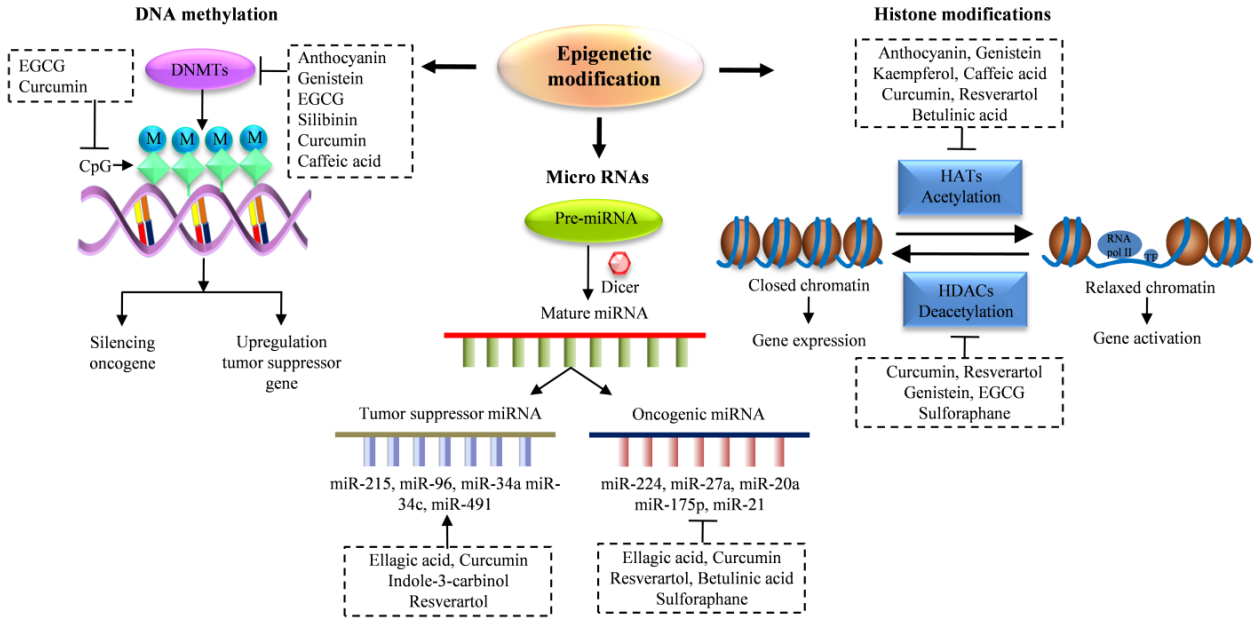
Inflammation
Proliferation
Invasion
Angiogenesis

Fig. 8.


DNA methylation
EGCG
Curcumin
DNMTs
Anthocyanin
Genistein
EGCG
Silibinin
Curcumin
Caffeic acid
CpG
M
Silencing oncogene
Upregulation tumor suppressor gene
Epigenetic modification
Micro RNAs
Pre-miRNA
Dicer
Mature miRNA
Tumor suppressor miRNA
miR-215, miR-96, miR-34a miR-34c, miR-491
Ellagic acid, Curcumin Indole-3-carbinol Resveratrol
Oncogenic miRNA
miR-224, miR-27a, miR-20a miR-175p, miR-21
Ellagic acid, Curcumin Resveratrol, Betulinic acid Sulforaphane
Histone modifications
Anthocyanin, Genistein Kaempferol, Caffeic acid Curcumin, Resveratrol Betulinic acid
HATs Acetylation
HDACs Deacetylation
Closed chromatin
Gene expression
RNA pol II
TF
Relaxed chromatin
Gene activation
Curcumin, Resveratrol Genistein, EGCG Sulforaphane