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Natural Compounds as Adjuncts for Treating Colon Cancer through Apoptotic Pathway

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ABSTRACT

Cancer is one of the deadliest diseases which is caused when abnormal cells divide uncontrollably and destroy body tissue. Colorectal cancer (CRC), also known as colon cancer, is one of the most common type of cancers in humans is closely linked to the global cancer – related mortalities worldwide. The ongoing clinical treatment for colorectal cancer or colon cancer largely engages surgery and chemotherapy. But as there are many side effects and due to emergence of drug resistance, it has become very necessary to find novel and more effectual drugs for colon cancer treatment. Chemo prevention, a novel method for controlling cancer encompasses the use of specific natural products or synthetic chemical agents to reverse, suppress or prevent premalignancy before the development of invasive cancer. Many studies have signified that various natural products have efficacious anti CRC effects and may be used as substitutional chemotherapy agents for CRC therapy. Various natural compounds have been shown to be promising on the basis of their anti cancerous effects and low toxicity. In this review we summarise the natural compounds having anti CRC effects from distinct sources. This review suggest that they provide a novel opportunity for treatment of colon cancer.

KEYWORDS: *Colon cancer, Apoptosis, Natural compounds, Caspases, Anti-cancer*

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INTRODUCTION

Cancer

Cancer is a crucial public health issue and the second prime cause of mortality globally. Cancer is a fatal disease whose progression occurs in many stages –normal cells get altered, development of tumour takes place and the tumour starts spreading to new areas of the body which is known as metastasis, that consist a chain of many events [Jemal et al., 2008]. A tumour can be malignant and benign. A malignant tumour can grow and spread to other parts of the body that means malignant tumours are cancerous while benign tumour only grows and doesn't spread to other parts of the body. There are a many number risk factors namely age, race and region which are involved in the development of cancer [Wiart 2007]. However cancer is a disease that can be cured.

Some recent research demonstrated that the dysfunctioning of certain genes which codes for the protein like receptors of growth factor, growth factors, inhibitor of tumour etc which account for the target of cancer treatment are the cause of most cancers [Glade 1999]. Cancer are of different types depend on in which part of the body it grows such as Carcinomas, Sarcomas, leukemia, and lymphomas.

Colon Cancer

Colon cancer refers to any malignant tumour appearing from the inner lining of colonic epithelium. It is the third most familiar malignancy globally, being often diagnosed in advanced stages. Basically colon cancer also known as rectal cancer, bowel cancer or colorectal cancer is the progression of cancer from the colon or rectum. There are numerous factors that are involved in the development of colorectal cancer such as insufficiency of physical activity [Watson et al., 2011], immoderate alcohol consumption [Huxley et al., 2009], old age [Schultz et al., 2010], family history [Johns et al., 2001], high-fat diets with no fiber and red meat, diabetes [Meyerhardt et al.,2003] and inflammatory bowel diseases , including ulcerative colitis and disease [Terzić et al., 2010]. The incident of colon cancer is mainly correlated with the occurrence aberrant crypt foci (ACF), an untimely neoplastic lesion which are mass of mucosal cells with an enlarged and thicker layer of epithelia than the nearby normal crypts that develop in to polyps followed by adenomas and adenocarcinomas [Board PDQATE et al., 2002].

Prohibition of colorectal cancer generally depends on screening methods to detect adenomatous polyps which are predecessor lesions to colon cancer [Schmoll et al., 2012]. The standard treatment of cancer is usually based on cytotoxic drugs, radiotherapy, chemotherapy and surgery [Reilly et al., 1997]. Except these treatments, antiangiogenic agents are also used for the cure and management of cancer development /Pasquier et al., 2004].

Colon cancer has various stages: 0, I, II, III and IV. Treatment for stages 0 to III generally includes surgery while for the stage IV and the recurrent colon cancer both surgery and chemotherapy are the choices. [Cappell 2007*].* Various chemotherapeutic drugs and diets have been suggested for the management of colorectal cancer based on the cancer stage and the patients characteristics [Schmoll et al., 2012]. The outcome of contrast between self proliferation and apoptosis determines colorectal tumour growth.

In order to make sure the evolution of colorectal cancer, many genetic variations are required in a sequential manner. The gene modification of TP53, KRAS, BRAF and PIK3CA play a very major role in colon cancer. There is a disturbance of signalling pathways caused by Gene modification, along with increment of proliferative potential and declined apoptosis. The three main epigenetic regulatory mechanisms are as follows (a) Histones modification (b) non coding RNA interference (c) Methylation of DNA [Samowitz et al., 2008].

Programmed cell death in normal and carcinogenic colon cells

Apoptosis is a suicidal procedure of cells in which the quantity of cells are controlled and cells having mutation or divergent cell cycle are eliminated. [Zimmermann et al., 2001]. Therefore, there is a great significance of explaining the apoptosis mechanism for malignant transformation, tumor eluding, and therefore for anti-cancer therapy. [Kimm et al., 2002; Kaufmann et al., 2003]. Malformation in apoptotic function results in the manner of development of colorectal cancer i.e. pathogenesis and radiotherapy and chemotherapeutics resistivity. [Watson et al., 2004].

Pathways of Apoptosis

Apoptosis is a form of programmed cell death. Apoptosis consist of different pathways named as metabolic pathways and biological pathways that has a very important role in the maintenance of an internal steady state within a define tissue of an organism known as tissue homeostasis and progression [Negrini et al., 2010]. Tumorigenesis may encouraged along with the initiation of resistance to cancer cells treatment due to apoptosis pathway regulation [Watson et al., 2004]. Various morphological features of the cells are showed by the apoptotic process such as : shrinkage of cell with nuclear fragmentation and condensation of chromatin, self fragmentation of cell and membrane blebbing .there are two fundamental signaling pathways which is responsible for the initiation of apoptosis: (a) the extrinsic pathway and (b) the intrinsic (or mitochondrial) pathway [Su et al., 2015]. Between the two apoptotic pathways there is an overlap: the intrinsic pathway also get activated by the extrinsic pathway, and with the recruitment and stimulation of caspases both the pathways get terminate. [Elmore et al., 2007; Taylor et al., 2008]. The protein apoptosis's caspase family is initiated and it cleaves the major components of cells which are required for the normal function of cells on receiving the particular signals which commands the cells to undergo apoptosis. [Hassan et al., 2009].

(A) The intrinsic pathway is also known as mitochondrial pathway. Intrinsic pathway is triggered by Certain cytotoxic drugs (sometimes known as antineoplastics), Deficiency of growth factor, damage of DNA, overloading of Ca2+ and activation of cancer causing genes [Hassan et al., 2009; Mendelsohn J et al., 2015]. The formation of the mitochondrial permeability transition pore (MPTP) initiates intrinsic pathway [Yang et al., 2009], which results in mitochondrial outer membrane permeabilization (MOMP). The osmotic distension of the matrix is instigated by the decrease in the mitochondrial membrane potential. Then an apoptosome complex is formed by the association of Cytochrome c with apoptotic protease apoptotic factor-1 (APAF-1) and caspase-9 .The cleavage of caspase-3 , initiation of endonuclease and fragmentation of nuclear DNA are the result of caspase-9 and/or caspase-8 activation, which is hallmark of apoptosis [Yang et al., 2009; Giansati et al., 2011]. The central regulators of intrinsic pathway are Bcl 2 family proteins (B cell leukaemia/lymphoma 2), which either repress or develop modification in permeability of mitochondrial membrane [Daniel et al., 2004].

(B)The extrinsic pathway when the ligand such as TNF (tumour necrosis factor), TRAIL (tumour necrosis related-apoptosis-inducing ligand) and CD95 (Fas or APO1) binds to their certain death receptors, then these death receptors get activated which ultimately initiates the extrinsic pathway of apoptosis [Locksley et al., 2001]. Death receptors are transmembrane proteins. In the cytosolic region of death receptor, a death domain is present. The oligomerization of these receptors is caused by the binding of ligands and then these receptors expose their death domains in their cytosolic tail. After then the binding between exposed death domain and Fas-Associated Death Domain (FADD) occurs. Various TNF- family receptors utilize the activation of caspase as a signaling mechanism [Ashkenazi et al., 1998; Walczak et al., 2000]. At the cytosolic domain of these receptors several intracellular proteins are recruited by the binding of these receptors at the cell surface. It results in the "death-inducing signaling complex" (DISC) formation, after which caspase-8 activation takes place [Kuwana et al., 2005; Hassan et al., 2014]. In the case of TNFR1, after the binding of ligand to TNFR1, the receptor's cytosolic region binds to TNFR1-associated death domain protein (TRADD adaptor), other signaling proteins instead of binding to FADD. Then, from the receptor initial complex is released, binding of TNFR1-associated death domain protein (TRADD) to Fas-Associated Death Domain (FADD) occurs in the cytoplasmic matrix, and the recruitment of caspase-8 takes place. Further interactivity takes place with proteins like FLICE-like inhibitory protein which forms the basis of downstream signaling, leading to the formation of a complex that contains caspase-8 and c-FLIP heterodimers which will suppress apoptosis. However, activation of caspase-8 takes place and cell undergoes apoptosis when the activity of NF-Kb is stopped or disrupted, or the expression of c-FLIP is suppressed. [Mendelsohn et al., 2015; Lavrik et al., 2005].

Apoptosis-based regulation in colon cancer treatment

Apoptosis is especially grouped into two pathways: the intrinsic and therefore the extrinsic pathway. The intrinsic pathway (mitochondrial pathway) can trigger the caspase cascade and results in apoptosis via the discharge of cytochrome [Roemer et al., 2007]. The extrinsic pathway initiates the activation of apoptosis by triggering cell death receptors (DRs), like FasL/CD95 L and TRAIL, on the cell surface [Fulda 2006; Dranoff et al., 2004] . Several natural products having an anticancer effect are mediated by the intrinsic apoptotic pathway. Natural products persuade apoptosis primarily by inducing the generation of ROS, reducing the mitochondrial membrane potential and the Bcl2/Bax ratio, and activating the related caspase proteins, which ultimately results in DNA fragmentation and apoptosis.

It has been found that Alkylresorcinols (ARs), extracted from wheat bran, stimulate cell cycle arrest and mitochondrial apoptosis by initiating and accumulating p53. AR C15 and AR C17 are found to downregulate the amount of Bcl2 and XIAP, and upregulate the amount of pro-apoptotic factors including cytochrome c, caspase 3/9, and PUMA in both HCT116 and HT-29 cells [Fu et al., 2018]. It has been found that Quercetrin from Toona sinensis leaves (QTL) persuade apoptosis by upregulating cytochrome c, Bax, Apaf-1, caspase-3/9. Moreover QTL has also been shown to activate ROS generation and persuade the dropping of mitochondrial membrane potential within the human CRC cell line SW620 [Zhang et al., 2017]. A prime bioactive compound named cardol extracted from Trigona incisa propolis, can trigger caspase-3, caspase-9, and PARP, and induce ROS generation in SW620 cells [Kustiawan et al., 2017]. Furthermore, 6-bromoisatin, extracted and identified from an Australian marine gastropod, Dicathais orbita, has been shown to induce apoptosis by prolong the expression of caspase-3 and -7 in both HT-29 and Caco-2 cells [Esmaeelian et al., 2013]. It has been found that a thiophene, 2-(Pro-1-ynyl)-5-(5,6-dihydroxypenta-1,3diynyl) thiophene (PYDDT), extracted from the roots of Echinops grijsii, stimulate mitochondrial-mediated apoptosis by regulating the amount of the related proteins, producing ROS, and activating ERK1/ 2 and JNK in SW460 CRC cells [Xu et al., 2015]. A completely unique compound isolated from the Chinese liverwort plant, Riccardin D, suppress the proliferation of HT-29 cells and initiate their apoptosis via the NF-κB signaling pathway [Liu et al., 2018]. A novel ent-kaurane diterpenoid, Pteisolic acid G isolated from Pteris semipinnata, has been found to inhibit the viability of HCT116 cancer cells, along with stimulating apoptosis via the generation of intracellular ROS, stimulation of p53, and downregulation of NF-κB p65 activity [Qiu et al., 2017]. The PI3K/Akt/mTOR signaling pathway is a crucial pathway; it has been reported that the dysregulation of this pathway is related to the proliferation, survival, metabolism, and drug resistance of CRC cells [Li et al., 2018; Porta et al., 2014; Bahrami et al., 2018].

There are many natural products that exert anticancer effects mediated by the extrinsic apoptotic pathway. Proanthocyanidins (Pcys) isolated from 11 berry species are shown to activate the extrinsic apoptosis pathway by triggering caspase-8 in SW620-TRAIL-resistant and SW480-TRAIL-sensitive CRC cells, which illustrate its potential to function an alternate to chemotherapeutic agents for CRC treatment [Minker et al., 2015]. It has been shown that Oplopantriol A, a compound extracted from Oplopanax horridus, has been shown to encourage apoptosis by the regulation of the related genes and TNF-mediated cell death pathways, including the TNF, FADD, TRADD, and caspase-3, -7, and -8 signaling pathways [Zhang et al., 2014] . It has been found that Calotroposid A, extracted from Calotropis gigantean and determined to be a terpenoid glycoside, activate the extrinsic apoptosis pathway by propagating the caspase-8 expression in WiDr carcinoma cells [Mutiah et al., 2018].

Furthermore, certain natural products can activate apoptosis via both the intrinsic and extrinsic pathways. A cyclic sesquiterpene, Zerumbone isolated from Zingiber zerumbet, can repress cell growth and promote cell apoptosis via the initiation of ROS and commencement of caspase3, -8, and -9 [Sithara et al., 2018]. It has been demonstrating that Mertensene, which is extracted from the red alga Pterocladiella capillacea, activate apoptosis by regulating the expression of caspases, PARP, and TRADD in HT-29 and LS174 cells. [Tarhouni-Jabberi et al., 2017].

Table 1: Natural products inducing apoptosis in colorectal cancer cells

Compounds	Source	Mechanism Of Action	References
Thiophene	Chinese liverwort plant	Upregulate cleaved caspase-3, -9 and the ratio of Bax/Bcl-2, block the NF-κB signaling pathway	[Liu et al., 2018]
Riccardin D	Grapes , peanuts, red wine, mulberries	Activation of caspase NF-kB suppression FasL elicitation MEK/ERK pathway initiation Downregulation of Bcl-2 Increment of ROS and p53 levels.	[Cagnol et al., 2010; Kong et al., 2008; Raj et al ., 2011; Cal et al., 2003; Panaro et al., 2012; Liu et al., 2003; Fouad et al., 2013]
Genistein	coffee , fava , Soyabeans, lupin, beans	Suppression of NF-Kb Initiation of Caspase PTK suppression AKT pathway prohibition downregulation of mdm2	[Banerjee et al., 2008; Nakamura et al., 2009]
Quercetin	seeds, nuts, tea, red wine, Fruits such as craneberry, black plumps, blueberry, apples , Vegetables such as capers, radish, leaves, dill, cilsntro, fennel, red onion, radicchio, kale	Downregulation of Bcl-2,EGFR, Cyclin D1, survive in inhibition Wnt/beta-catenin signalling pathway prohibition Increase in ROS and p53 levels MEK/ERK pathway stimulation	[Kim et al., 2008; Cagnol et al., 2010; Kong et al., 2008; Raj et al ., 2011; Fridrich et al., 2008]
2-(Pro-1-ynyl)-5-(5,6-dihydroxypenta-1,3diynyl)	Roots of Echinops grijsii	ROS-Mediated JNK Activation	[Xu et al., 2015]

Curcumin	Turmeric, curry, mustard	NF-κBinhibition ROSinduction Modulation of MAPK pathwayDownregulationofsurvivinandIGF-1 expression	[Yogosawa et al., 2012; Tu et al., 2015; Camacho-Barquero et al., 2007; He et al., 2011; Li et al., 2015]
Mertensene	Red alga Pterocladiella capillacea	Activate caspase-3 and PARP cleavage and increase TRADD	[Tarhouni-Jabberi et al., 2017]
Apigenin	Chamomile tea, Parsley, celery, Dandelion, coffee.	Alteration of survival and death effectors (Mcl-1,P13K, STAT3, JNK, ERK,AKT)	[Shao et al., 2013; Turktekin et al., 2011]
Zerumbone	Zingiber zerumbed	Induce ROS, activate caspase-3/8/9 and downg regulate Bcl2	[Sithara et al., 2018]
Silibinin	Milk thistle seeds	Down regulation of Bcl-2 up regulation of Bax cyclin D1and c-myc expression decline death receptors DR4,DR5 up regulation	[Rajamanickam et al., 2008; Kaur et al., 2010; Velmurugan et al., 2010; Kauntz et al., 2012; Raina et al., 2013]
Calotroposid A	Calotropis gigantean	Increase caspase-8	[Mutiah et al., 2018]
Naringenin	Grape, oranges and tomatoes (skin)	mitochondrial membrane potential drop initiation of Caspase-3 production of Intracellular ROS Sustained ERK activation	[Lee et al., 2008; Totta et al., 2004]
Oplopantriol A	Oplopanax horridus	Up regulate TNFRSF10A, TNF, TNFSF8, CRADD, FADD, TRADD, caspase-3, -7 and -8	[Zhang et al., 2014]
Pomegranate juice	Pomegranate	Bcl2-XL down regulation Initiation of Caspase-3 and caspase-9 Suppression of NF-Kb AKT Pathway inhibition	[Adhami et al., 2009; Jaganathan et al., 2014; Adams et al., 2006; Larrosa et al., 2006]
Alkylresorcinols	Wheat bran	Decrease Bcl2 and XIAP, increase PUMA, cytochrome C, cleaved caspase-9 and -3	[Fu et al., 2018]
Sulphoraphane	mustard, turnip, radish, arugula, watercress Broccoli, , cauliflower, Brussels sprouts, cabbage, collards, kohlrabi	Bax, p21 Upregulation G_2/M cell cycle arrest	[Grabacka et al., 2014; Zeng et al., 2011; Ho et al., 2009; Myzak et al., 2006]
Cardol	Trigona incisa propolis	Increase caspase-3, caspase-9, cleavage of pro-caspase-3 and pro-caspase-9, PARP and ROS	[Kustiawan et al., 2017]
Pteisolic acid G	Pteris semipimmata	Downregualte NF-κB p65 activity, stimulate p53 and promote ROS production	[Qiu et al.,2017]
Lycopene	Watermelons, Tomatoes, papayas and red carrots	upregulation of Bax and FasL downregulation of Bcl-2 and Bcl-XL Akt,NF-K b downregulation	[Huang et al., 2015; Trejo-Solis et al., 2013]

There are various natural compounds that shows a broad variety of biological exertion, encompassing anti-inflammatory and cytoprotective activities, and many of them behave as anti-cancer reagents. Curcumin, genistein, tea polyphenols such as epigallocatechin, gallate, resveratol, sulforaphane broccoli, isothiocyanates, silymarin, diallyl sulphide, rosemarinic acid, gingerol and quercetin have great anti oxidant activities, and showed anti-proliferative results in case of different cancer cell lines [Fulda et al., 2010].

Resveratrol (RSV, trans-3, 4'trihydroxystilbene) is a polyphenol phytoalexin. It is a naturally occurring compound which is found in large amount in many plants and their products such as grapes and red wine, mulberries, etc. Resveratrol has shown effect against inflammation, tumorigenesis, aging, and virus. It also shows effect in protecting the heart and nerve cells from dysfunction or damaged. [Zhang et al., 2012; Castillo-Pichardo et al., 2012]. Prohibiting proliferation of cells, induction of programmed cell death (apoptosis), declination in development of new blood vessels (angiogenesis), and causing cell cycle arrest, Resveratrol has illustrated anti-colon cancer properties [Mahyar-Roemer et al., 2002; Cal et al., 2003].

Genistein (GST 4',5,7-trihydroxyisoflavone), a compound which occurs naturally whose main source is soyabeans, coffee, lupin, fava beans, and is abundantly present in soy products [Nicastro et al., 2012]. Similar to etoposide and doxorubicin, genistein is an active suppressor of topoisomerase. Genistein is responsible of wide varieties

of activity. It shields the normal cells from their modification into malignant transformation, it protects cancer cells proliferation and declaration [Banerjee et al., 2008; Nakamura et al., 2009].

Quercetin (QCT, 3, 3', 4',5,7-pentahydroxyflavone) is a significant dietary flavonoid, which is found in various vegetables such as carpers, leaves of raddish, fennel, red onion etc, fruits such as apples, craneberry, black plums etc, it can also be found in tea, red wine and seeds. Quercetin also takes part in the inhibition of processes related to tumor, which includes the phenomenon caused by an imbalance of free radical and antioxidants in the body i.e. oxidative stress, cellular proliferation and spreading of tumour cells to the new areas or parts of body known as metastasis. Whether then acting on cells which are normal and non-transformed, quercetin has a precise activity on the cell lines of tumour by acting as pro apoptotic flavonoid [Sanchez-Gonzalez et al., 2011]. The suppression of the expression of survivin and Cyclin D (1) along with the suppression of Wnt/beta-catenin signalling pathway was correlated with the anti tumour effect which was established in cell line SW480 of colorectal cancer [Shan et al., 2009].

Curcumin (CRM, 1,7-bis-(4-hydroxy-3-methoxyphenyl1)-1,6-heptadiene-3,5-dione) is a biphenyl lheptanoid (also known as diarylheptanoid). It is the major turmeric's curcuminoid, which is isolated from *Curcuma longa.* Besides its antioxidant properties it also exhibits effects against inflammation. In the HT-29 and HCT-15 cell lines of human colorectal cancer, curcumin actively inhibits the proliferation of cells [Kawamori et al., 1999; Jhonson et al., 2007].

Apigenin (APG, 4", 5, 7-trihydroxyflavone) is one of the most frequently found flavonoids which is extensively found in many fruits and vegetables. Nevertheless, towards cancer cells, an un pretentious anti tumour activity was merely showed by Apigenin. There is a need to promote the anti-tumour effectiveness of apigenin by introducing the novel strategies [Shao et al., 2013].

Lycopene is a tetraterpenoid pigment and is a chemical which is produced by plants through primary and secondary metabolism (phytochemical). Some major source of lycopene involved watermelons, red carrots, tomatoes etc. Even though Lycopene is chemically a photosynthetic pigment important for photosynthesis i.e. carotene, there is an absence of vitamin A activity in it. Some foods which are not red in colour also have a presence of lycopene like parsley. Lycopene is an active carcinopreventive agent. Threat of Different categories of human cancer which also involve colorectal cancer can be reduced by intake or eating tomatoes [Tang et al., 2008; Lin et al., 2011].

Pomegranate juice is attained from *Punica granatum.* Pomegranate juice owns precise activity against parasites, microbes, inflammation and carcinogen [Akpinar-Bayizit et al., 2012]. In the preclinical studies of animal, the progression of several type of cancer including colorectal cancer, prostate cancer, lung cancer and skin cancer was prohibited by the oral intake of extract of pomegranate [Adhami et al., 2009]. By the intrinsic pathway activation, the derivative of pomegranate juice was illustrated was shown to endorse programmed cell death (apoptosis) of colorectal cancer cells, however there was no consequences on the extrinsic pathway [Jaganathan et al., 2014].

Naringenin (5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-1) is a type of flavanoid (flavanone). As an antioxidant, initiator of metabolism of carbohydrate, controller or regulator of immune system and forager of free radical, Naringenin has depicted a bioactive result on wellbeing of human. [Lee et al., 2008].

Silibinin is also called as silibin. It ia a very important component of **silymarin**, a flavonolignans isolated from the milk crystal seeds. It was depicted that in the cells of colorectal cancer apoptosis was initiated by silibinin [Kaur et al., 2010; Kauntz et al., 2012].

Glucobrassicin is found in cabbages, broccoli, mustards, horseradish and woad. Myrosinase is responsible for the degradation of indole-3-carbinol (main hydrolysis product subsequent to glucobrasscin), which shows apoptosis-triggeringg effect in concentration-and time-dependent manner colorectal cancer cells of human [Bonnesen et al., 2001; Zheng et al., 2002].

Conclusion

Cancer is a crucial public health issue and the second prime cause of mortality globally. The insufficiency of suppression of the whole cellular population of tumour and the chemo resistance subsequent progression is a major provocation for flourishing colorectal cancer cure. Natural products have been confirmed to exert undoubted advantages and have potential use for cancer treatment. Natural products are potentially capable to hinder growth and proliferation of colorectal cancer cells. Contrast data of several natural compounds having anti cancer effect in colorectal cancer are available. The results of oncolytic drug can be persuaded against the colorectal cancer cell development and apoptosis by these natural compounds having anticancer effects. Natural products such as grains, cereals, fruits, vegetables, medicinal plants and their various phytochemical constituents confer protective effects against wide range of cancers including colorectal cancer (CRC). On the basis of apoptosis related anticancer effects certain compound were shown to be promising when the wide variety of natural compounds were investigated. Chemoprevention strategies is represented by the utilization of natural occurring compounds that play a major role in the hindrance of cancer development, obstruct stimulation, reduced caspase activity, or persuade inhibition or reversal of carcinogenesis at a premalignant stage. Natural compounds usage in treating colon cancer leads to disruption of balance between pro- and anti-apoptotic proteins, altered redox status in apoptosis induction and impaired death receptors signalling. In this review, it has been summarized the recently explored natural products that have been used or have great potential for use in the treatment of colorectal cancer (CRC).

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