

Potential proapoptotic phytochemical agents for the treatment and prevention of colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is one of the leading causes of mortality among men and women. Chemo-resistance, adverse effects and disease recurrence are major challenges in the development of effective cancer therapeutics. Substantial literature on this subject highlights that populations consuming diets rich in fibers, fruits and vegetables have a significantly reduced incidence rate of CRC. This chemo-preventive effect is primarily associated with the presence of phytochemicals in the dietary components. Plant-derived chemical agents act as a prominent source of novel compounds for drug discovery. Phytochemicals have been the focus of an increasing number of studies due to their ability to modulate carcinogenic processes through the alteration of multiple cancer cell survival pathways. Despite promising results from experimental studies, only a limited number of phytochemicals have entered into clinical trials. The purpose of the current review is to compile previously published pre-clinical and clinical evidence of phytochemicals in cases of CRC. A PubMed, Google Scholar and Science Direct search was performed for relevant articles published between 2008-2018 using the following key terms: 'Phytochemicals with colorectal cancers', 'apoptosis', 'cell cycle', 'reactive oxygen species' and 'clinical anticancer activities'. The present review may aid in identifying the most investigated phytochemicals in CRC cells, and due to the limited number of studies that make it from the laboratory bench to clinical trial stage, may provide a novel foundation for future research.

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in men and women and is the fourth leading cause of cancer-associated mortality worldwide (1). In 2018, >30,000 CRC-associated mortalities were reported in the USA (2). According to the World Health Organization, in 2008, 1.2 million new CRC cases were reported globally (3). Annually >0.6 million patients succumb due to CRC (4), and a family history of CRC or chronic inflammatory bowel disease is a contributing factor for disease progression (5). Additionally, a sedentary lifestyle, low physical activity and unhealthy dietary patterns, including diets with low fiber and a high content of red meat or fat, cigarette smoking and alcohol abuse, are the major causes of CRC development. The majority of CRC cases are diagnosed at the advanced stages of disease, which makes curative treatment impossible (6).

Understanding the developmental pathways in tumor cells that promote the growth and metastasis of tumors is important in order to identify the molecular targets of cancer therapeutics. The majority of CRC cases occur as a result of genetic and epigenetic modifications (7-9). Studies investigating human cancer, including CRC, have demonstrated a central role of p53 in tumor suppression (10). Almost 50% of CRC cases are reported to have a mutation in p53 (9), which promotes cell proliferation, invasion, metastasis and resistance to a variety of anticancer drugs, such as 5 fluorouracil (11,12). Mutations in the KRAS, BRAF and neuroblastoma RAS viral oncogene genes have also been reported in CRC (13). Additionally, mutations of the adenomatous polyposis coli gene in CRC

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promotes the dysfunction of β -catenin and activates the Wnt pathway, which is an activator of the key cell cycle regulatory genes cyclin D1 and c-Myc, which provide suitable conditions for cellular proliferation (13). In CRC, the activation of NF- κ B upregulates a number of genes responsible for the generation of pro-inflammatory mediators and cytokines, which are essential for CRC cell propagation (14). Additionally, the PI3K/Akt pathway promotes tumor proliferation via inhibition of apoptosis and stimulation of the cell cycle (15).

High levels of reactive oxygen species (ROS) have been detected in almost all types of cancer and been demonstrated to potentiate numerous aspects of tumor development and progression. Under physiological conditions, the intracellular ROS levels are not high enough to induce cell damage. However, any imbalance in the redox status of the cell results in oxidative stress, which exerts an important function in the initiation, promotion and progression of carcinogenesis (16). Physical agents, chemical agents, inflammation and infection potentiate oxidative stress, which directly damages DNA and promotes tumorigenesis (17). Under mild oxidative stress, wild-type p53 is reported to induce the expression of antioxidant enzymes, and stimulates cell repair and survival mechanisms (18,19). However, upon acute oxidative stress, p53 reduces the expression of detoxifying enzymes and stimulates apoptosis (20). By contrast, mutated p53 exhibited in cancer cells cannot induce the expression of antioxidant enzymes to detoxify higher levels of ROS, whereas it upregulates cell proliferative gene expression, which promotes the propagation of DNA damage (21).

Apoptosis is a tightly regulated mechanism of cell death and a stress response to toxic stimuli that is required to maintain intestinal epithelial cell homeostasis. Spontaneous apoptosis continuously occurs in the normal, unstressed intestine and stress-induced apoptosis occurs following genotoxic insult, including exposure to DNA-damaging agents. In cancer cells, dysregulation of the apoptotic process results in disturbance of tissue homeostasis, which then results in uncontrolled proliferation of cells (22). Caspases function as initiators and executors of apoptosis. Initiator caspases, including caspase-8 and -9, which are involved in the extrinsic and intrinsic apoptotic pathways, activate effector caspases, including caspase-3 and -7, which cleave several proteins, including poly(ADP ribose) polymerase-1 (PARP-1) in cells (23,24). PARP-1 is a nuclear enzyme involved in DNA repair, DNA stability and transcriptional regulation. PARP-1 cleavage prevents recruitment of enzymes to the site of DNA damage and is considered to be a hallmark of apoptosis (Fig. 1) (25).

The endoplasmic reticulum (ER) is responsible for the synthesis, folding and maturation of proteins (26). Conditions that result in ER stress can activate cell protective mechanisms; however, if the stress is excessive or prolonged then it will eliminate cells via the intrinsic apoptosis pathway (26). This switch between pro-survival and pro-apoptotic pathways is due to the induction of a transcriptional factor C/EBP homologous protein (CHOP) (27), which has been reported to downregulate the anti-apoptotic protein Bcl-2 (28). Additionally, ER stress increases intracellular calcium (Ca^{2+}) levels, which activates calpain-induced cleavage of anti-apoptotic B-cell lymphoma-extra large (Bcl-xl) and increases caspase-12 activity, which then activates caspase-9

independent of apoptotic protease activating factor 1 (Apaf-1), followed by the activation of caspase-3 (Fig. 1) (29,30).

The activation of apoptosis is an important mechanism for CRC prevention and treatment (31-33). Dietary phytochemicals are known to prevent the initiation of carcinogenesis via the induction of antioxidant enzymes and block the progression of carcinogenic cells via the induction of apoptosis and cell cycle arrest (34,35). Almost 50% the approved anticancer drugs are derived from natural products or their derivatives (36,37). To establish novel compounds that can be utilized in combined therapy to potentiate the effect of chemotherapeutic drugs, a number of studies have been performed to identify agents present in diet or herbs that interfere with proliferative cell signaling pathways (34-38). The aim of the present study was to compile available literature published between 2008-2018 regarding the mechanisms of apoptosis induced by phytochemicals in CRC cells in preclinical and clinical settings. This may assist in providing a solid foundation for future research options in this field.

2. Literature review method

The present review is based on a literature search of PubMed (ncbi.nlm.nih.gov/pubmed/), Google Scholar (scholar.google.com/) and Science Direct (sciencedirect.com/) to identify relevant studies published between 2008-2018. The search was performed with the following key terms: 'Phytochemicals with colorectal cancers', 'apoptosis', 'reactive oxygen species (ROS)' and 'clinical anticancer activities'. Only studies investigating the effects of phytochemicals on patients with CRC in preclinical and clinical trials were included in the present review.

3. Apoptosis-inducing phytochemicals in CRC

Phytochemicals are a non-nutritive group of compounds naturally present in fruits, vegetables, spices, grains and herbs, which have health promoting and disease preventing characteristics (39). In preclinical and clinical studies of different types of tumor, the consumption of fruits and vegetables has been reported to exert beneficial health effects (39,40). CRC is strongly associated with dietary factors and the association of phytochemicals with CRC prevention has been reported in several studies (41-43). Numerous phytochemicals exhibit chemo-preventive effects in CRC due to their antioxidative and ROS scavenging activities. However, various phytochemicals are also known to induce apoptosis by promoting ROS generation (44-62). Table I details a list of ROS-inducing phytochemicals in CRC.

The induction of apoptosis and inhibition of tumor cell proliferation by cell cycle arrest are markers for the evaluation of phytochemical anticancer activities. Table II details a list of phytochemicals that can induce CRC cell cycle arrest at different phases of the cell cycle (45,48,51,54,55, 57,59,60,63-84). Phytochemicals are classified according to their chemical structure, for example, carotenoids, alkaloids and phenolic compounds such as flavonoids, phenolic acid, stilbenes (resveratrol), curcuminoids, tannins and coumarins (85). The following sections discuss the apoptotic mechanisms of different classes in detail.

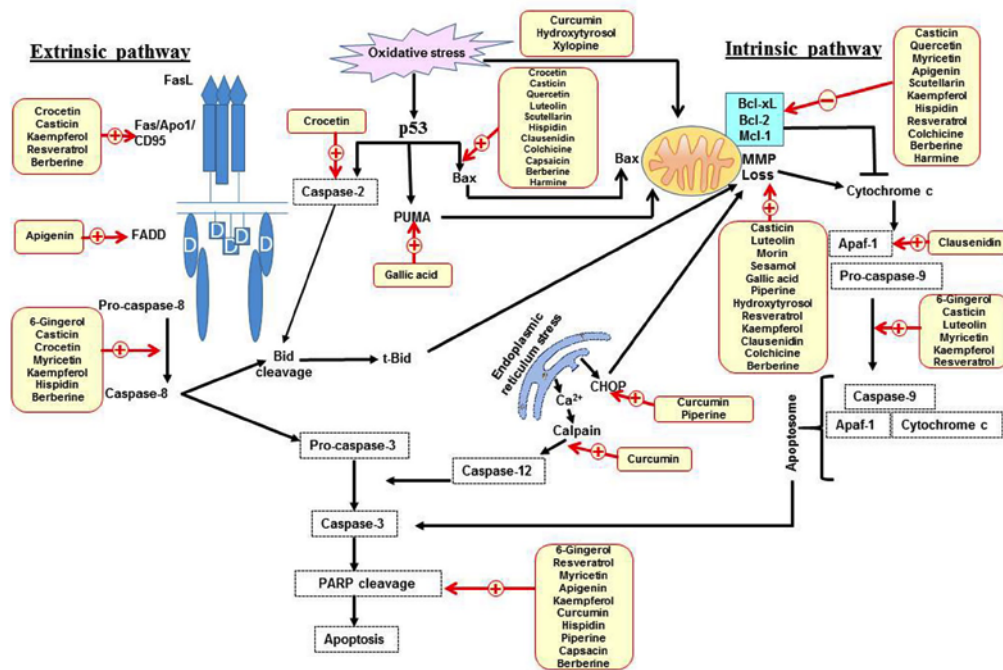


Figure 1. Signaling pathways of apoptosis and molecular targets of phytochemicals. Depending on the cell type and status of p53, phytochemicals can induce apoptosis by regulating targets of the extrinsic and intrinsic apoptosis pathways shown in black arrows. Red arrows indicate effects of phytochemicals on different apoptosis targets. Phytochemicals with activating and inhibiting activities are shown with + and - symbols, respectively. FasL, Fas ligand; FADD, Fas-associated death domain; PUMA, p53 upregulated modulator of apoptosis; PARP, poly(ADP ribose) polymerase-1; CHOP, C/EBP homologous protein; Bcl-xL, B-cell lymphoma-extra large; Mcl-1, myeloid cell leukemia sequence-1; Apaf-1, apoptotic protease activating factor 1.

4. Carotenoids

Carotenoids are colored lipid soluble pigments present in plants, fungi, bacteria and algae, and also have been identified in numerous foods, including fruit, vegetables and fish. Carotenoids are responsible for providing bright coloration to plants and animal. There are >600 carotenoids with natural structural variations, which are divided into lycopenes, β -carotenes, luteins and zeaxanthins (86).

Carotenoids are the most characteristic and important components present in saffron (*Crocus sativus* L.) stigmas. In ancient times, the Arabs, Indians and Chinese used carotenoids for the treatment of various diseases, including cancer. Crocetin is the most potent carotenoid in saffron (86,87). Crocetin can induce different apoptotic mechanisms in colon cancer cells with varying p53 statuses. The presence of wild-type p53 in HCT 116 cells trans-activates Bax along with upregulation of p53-induced death domain protein, which cleaves and activates Bid via caspase-2 (88). However, in functional p53-impaired cells (HCT 116 p53^{-/-}), augmentation of the p53-paralogue p73 was observed, which upregulates Fas to cleave Bid through the Fas-associated death domain (FADD)-caspase-8-pathway (88).

5. Phenolic compounds

6-Gingerol. Ginger contains numerous phenolic compounds, including 6-gingerol, 6-shagol, 6-paradol and zingerone (89). Among these compounds, 6-gingerol has been extensively

investigated for its cytotoxic effects in various types of cancer, including colon cancer (83,84). 6-gingerol inhibits the proliferation of SW480 colon cancer cells by arresting them at the G₂/M phase and induces apoptosis via activation of caspase-8, -9, -3 and -7 and PARP cleavage (75).

Flavonoids. Flavonoids are one of the largest groups of naturally-occurring phenols, including flavones, flavanols, isoflavones, flavonols, flavanones and flavanonols (90). Flavonoids are present in fruits, vegetables, grains, bark, roots, stems, flowers, tea and wine. Along with carotenoids, they are responsible for the vivid colors in fruits and vegetables (91). Flavonoids are known for their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties (91).

Casticin, a flavonoid derived from the natural plant *Fructus Vitis*, has been demonstrated to exert its apoptotic effect in colo 201 cells by arresting cells at the G₂/M phase. Casticin increases ROS production, decreases the expression of matrix metalloproteinases, increases the release of cytochrome c from the mitochondria and triggers the activation of caspase-8, -9 and -3. Additionally, increases in tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), Fas, Fas ligand (FasL) and FADD have been observed following treatment with casticin (55). Furthermore, casticin upregulates the pro-apoptotic proteins Bax, BH3 interacting domain death agonist (Bid) and Bcl-2 antagonist/killer, and downregulates Bcl-2 and Bcl-xL, which induces apoptosis via the extrinsic and intrinsic apoptotic pathways (55).

Table I. Reactive oxygen species-inducing phytochemicals.

Compound	Origin	Cell line(s) investigated	(Ref.)
p-Methoxycinnamic acid	Rice bran, turmeric, <i>Kaempferia galangal</i> and brown rice	HCT-116	(44)
Piperine	<i>Piper nigrum</i> and <i>Piper longum</i>	HRT-18	(45)
Apigenin	Fruits and vegetables, including parsley, onions, oranges, tea, chamomile, wheat sprouts and certain seasonings	HT-29 and HCT-15	(46)
Curcumin	<i>Curcuma long</i>	HCT-116	(47)
Curcumin	<i>Curcuma long</i>	HT-29	(48)
Emodin	Natural herbs, including <i>Rheum palmatum</i> and <i>Polygonum</i>	SW480 and SW620	(49)
Quercetin	Fruits, vegetables, nuts and red wine	HT-29	(50)
Patulin	Molds, apple, peaches, pears and grains	HCT-116	(51)
Resveratrol	Grapes, mulberries, peanuts and red wine	HCT29 and COLO201	(52)
Salinomycin	<i>Sanguinaria Canadensis</i> root and species containing poppy-fumaria alkaloids	HCT-116	(53)
Bigelovin	<i>Inula helianthus-aquatica</i>	HT-29 and HCT 116	(54)
Casticin	<i>Fructus Viticis</i>	colo 205	(55)
Morin	Leaves of common guava, onion, almond and members of the <i>Moraceae</i> family, including mulberry, figs and Chinese herbs	SW480	(56)
Sesamol	Sesame seeds	HCT116	(57)
Gallic acid	Oak, <i>Drosera</i> , golden root, stinging nettle, Chinese mahogany and dietary substances, including bearberry, blackberry, chocolate and walnut	HCT15	(58)
Hispidin	<i>Phellinus linteus</i>	CMT-93 and HCT116	(59)
Clausenidin	<i>Clausenidin excavata</i> Burm. f.	HT-29	(60)
Colchicine	<i>Colchicum autumnale</i> and <i>Gloriosa superba</i>	HT-29	(61)
Xylopin	<i>Xylopia laevigata</i>	HCT116	(62)

Table II. Cell cycle-arresting phytochemicals.

Compound	Origin	Cell line(s) investigated	Cell cycle phase(s)	(Ref.)
Artocarpin	<i>Artocarpus heterophyllus</i>	HT-29	G ₁	(63)
Silibinin	<i>Silybum marianum</i>	LoVo	G ₁ and G ₂ /M	(64)
Piperine	<i>Piper nigrum</i> and <i>Piper longum</i>	HRT-18	G ₀ /G ₁	(45)
Piperine	<i>Piper nigrum</i> and <i>Piper longum</i>	HT-29	G ₁	(65)
Vicenin-2	<i>Ocimum sanctum</i> Linn and <i>Moringa oleifera</i>	HT-29	G ₂ /M	(66)
Curcumin	<i>Curcuma longa</i>	COLO	G ₀ /G ₁	(67)
Curcumin	<i>Curcuma longa</i>	320DM	S	(68)
Curcumin	<i>Curcuma longa</i>	HT-29	G ₂ /M	(48)
Patulin	Molds, apple, peaches, pears and grain	HCT116	G ₂ /M	(51)
Resveratrol	Grapes, mulberries, peanuts and red wine	HCT-116 and Caco ₂	G ₁ /S	(69)
Bigelovin	<i>Inula helianthus-aquatica</i>	HT-29 and HCT 116	G ₂ /M	(54)
Plumbagin	<i>Plumbago zeylinica</i>	HCT116	G ₁	(70)
Cucurbitacin-I	Cucurbitaceae species	SW480	G ₂ /M	(71)
Crocin	<i>Crocus sativus</i> L. (Saffron)	HCT116 wild-type	G ₀ /G ₁	(72)
Crocin	<i>Crocus sativus</i> L. (Saffron)	HCT116 p53(-/-)	G ₂ /M	(72)
Crocetin	<i>Crocus sativus</i> L. (Saffron)	SW480	S	(73)
Ginkgetin	<i>Ginkgo biloba</i> and <i>Dioon</i>	HCT116	G ₂ /M	(74)
Casticin	<i>Fructus Viticis</i>	colo 205	G ₂ /M	(55)
6-Gingerol	Ginger	SW480	G ₂ /M	(75)
Quercetin	Fruits, vegetables, nuts and red wine	HT-29	G ₀ /G ₁	(76)
Kaempferol	Fruits and vegetables	HT-29	G ₁ and G ₂ /M	(77)
Sesamol	Sesame seeds	HCT116	S	(57)
Hispidin	<i>Phellinus linteus</i>	CMT-93 and HCT116	Sub G ₁	(59)
Hydroxytyrosol	Virgin olive oil	Caco ₂ and HT29	G ₁	(78)
Hydroxyphenylpropionic	Virgin olive oil	Caco ₂ and HT29	G ₂ /M	(78)
Phenylacetic	Virgin olive oil	Caco ₂	G ₂ /M	(78)
Catechol	Virgin olive oil	Caco ₂	S	(78)
Clausenidin	<i>Clausenidin excavata</i> Burm. f.	HT29	G ₀ /G ₁	(60)
Xylopine	<i>Xylopi laevigata</i>	HCT116	G ₂ /M	(62)
Capsaicin	Red hot pepper	HCT116	G ₀ /G ₁	(79)
Capsaicin	Red hot pepper	LoVo	G ₀ /G ₁	(80)
Berberine	<i>Berberis</i> and <i>Coptis</i>	SW480	G ₀ /G ₁	(81)
Berberine	<i>Berberis</i> and <i>Coptis</i>	HCT-8	S	(82)
Berberine	<i>Berberis</i> and <i>Coptis</i>	LoVo	G ₂ /M	(83)
Harmine	<i>Peganum Harmala</i>	SW620	S and G ₂ /M	(84)

Quercetin is a major dietary flavonoid that has been identified in a wide range of fruits, vegetables and beverages, including tea and wine. Quercetin is known for its antioxidant, anti-inflammatory and anti-proliferative properties (50). In HT-29 colon cancer cells quercetin treatment decreases cell viability, arrests the cell cycle at the G₁ phase and induces apoptosis (76,92). Quercetin inhibits the PI3K-mediated cell survival signaling pathway via phosphorylation of its downstream target Akt (92). Additionally, quercetin decreases the expression of COP9 signalosome subunit 6 (CSN6), a subunit of the constitutive photomorphogenesis 9 multiprotein complex (76). Akt is a known regulator of CSN6, which promotes carcinogenesis by stabilizing the viral oncogene homolog Myc (76). Furthermore, quercetin-treatment targets

CSN6 genes to induce apoptosis, as it downregulates Myc and Bcl-2 expression, and increases the expression of p53 and Bax (76,92). Quercetin has also been demonstrated to suppress the Wnt/ β -catenin and NF- κ B pathways in CRC cells (93,94). Additionally, treatment of HT-29 cells with quercetin upregulates AMP-activated protein kinase, a physiological cellular energy sensor, which markedly suppresses cell proliferation (92).

Luteolin (3',4',5,7-tetrahydroxyflavone) is a common flavonoid that exists in numerous types of plants including fruits, vegetables and medicinal herbs (95). Plants rich in luteolin have been used in Chinese traditional medicine for the treatment of various diseases, including hypertension, inflammatory disorders and cancer (95). Luteolin decreases the cell

viability of HT-29 cells without affecting normal colon cells and it has been observed to induce apoptosis of HT-29 cells by activating the mitochondria-mediated caspase pathway (96). Treatment of HT-29 cells with luteolin results in a loss of the mitochondrial membrane potential, an increase in mitochondrial Ca^{2+} level, upregulation of Bax, downregulation of Bcl-2, release of cytochrome *c* from the mitochondria to the cytosol and an increase in the levels of the active forms of caspase-9 and caspase-3 (96).

Morin is a flavonoid primarily identified in the leaves of common guava, onion and almonds, and in members of the Moraceae family, including mulberry, figs and Chinese herbs. The pro-oxidative effect of morin in SW480 cells results in a disturbance of the mitochondrial function, which results in the activation of the intrinsic and the extrinsic apoptosis pathways (56). Additionally, morin induces a significant reduction in glucose transporter-1 expression, which results in a decline in cellular glucose uptake, resulting in an impaired mitochondrial function, which further sensitizes cells to undergo apoptosis via the intrinsic apoptosis pathway (56).

Scutellarin is a flavonoid isolated from a medicinal herb *Scutellaria barbata* D. Don. Scutellarin is widely used in Korea and South China to treat cardiovascular, neurological and inflammatory diseases (97). In colon cancer cells, scutellarin downregulates the anti-apoptotic protein Bcl-2 and induces apoptosis by activating p53, which upregulates Bax to activate caspase 3 via the mitochondrial pathway (97).

Myricetin is a flavonoid present in fruits, vegetables, tea, berries and medicinal plants (98). Myricetin has been reported to exhibit anticancer activity in the colon cancer HCT-115 cells via activation of nucleoside diphosphate kinase, which has been reported to induce apoptosis and inhibit metastasis in various types of cancer, such as hepatocellular carcinoma and pancreatic cancer (99,100). Additionally, myricetin activates caspase-3, -8 and -9, and PARP, and downregulates the anti-apoptotic Bcl-2 protein to induce apoptosis in colon cancer cells (98).

Apigenin is a common flavonoid present in numerous plants, fruits and vegetables. The primary source of its consumption is chamomile tea, which is prepared from dried flowers of *Matricaria chamomilla* (101). Apigenin has been reported to exert anti-proliferative and anti-metastatic effects in a variety of CRC cell lines, such as those for lung cancer and osteosarcoma (102,103). Additionally, apigenin has been demonstrated to inhibit the Wnt/ β -catenin signaling pathway (101,103) and suppress the phosphorylation of STAT3 (104), which in turn results in the downregulation of the anti-apoptotic proteins Bcl-x1 and myeloid cell leukemia sequence-1 (Mcl-1), which stimulates the cleavage of PARP and the apoptosis of colon cancer cells (104). Furthermore, an *in vivo* study revealed that apigenin increases the apoptotic index of SW480 colon cancer cells via an upregulation of FADD (101).

Kaempferol is a flavonol present in fruits and vegetables, including apples, onions, and green and black tea (105). A high intake of kaempferol has been reported to reduce the risk of colon cancer (105). Kaempferol induces apoptosis of HT-29 colon cancer cells via activation of the extrinsic and intrinsic apoptosis pathways. Kaempferol initiates the extrinsic apoptosis pathway by increasing the level of FasL, which binds

with the Fas receptor and activates caspase-8. Caspase-8 then cleaves Bid and interacts with the intrinsic apoptosis pathway via translocation of t-Bid to the mitochondria, as evident by the release of cytochrome *c*, activation of caspase-9, -7 and -3, and PARP cleavage (106). Additionally, kaempferol decreases the expression of the anti-apoptotic protein Bcl-x1 and reduces Akt activity (106).

Curcuminoids. Curcumin, a derivative of turmeric (*Curcuma longum*), is a widely investigated phenolic compound that possesses potent anti-inflammatory, antioxidant and anti-cancer properties (107). It has previously been reported that curcumin induces apoptosis in human colon cancer HT29 cells via the calpain/caspase-12 apoptotic pathway (48). A previous study demonstrated that curcumin induces ROS generation in p53 mutated HT-29 cells, which results in cell cycle arrest and apoptosis via activation of the ROS-mediated mitochondrial pathway (47). Furthermore, curcumin induces caspase-3-mediated PARP cleavage in p53^{+/+} and p53^{-/-} HCT116 cells, which indicates that the p53 status does not interfere with the ability of curcumin to induce apoptosis (47). In recent *in vitro* and *in vivo* studies, co-treatment of curcumin with TRAIL increased TRAIL-induced apoptosis via an upregulation of death receptor 4 and 5 (108). Additionally, in chemo-resistant CRC cells curcumin enhanced the potential of conventional chemotherapeutic drugs via inhibition of drug induced proliferative targets, including cyclin D1, NF- κ B, PI3K and Src (109,110).

Sesamol. Sesamol is a phenolic compound present in sesame seeds that has been extensively investigated in different types of cancer, such as hepatocellular carcinoma and skin tumors (111,112). However, to the best of our knowledge, only a single study has been performed with CRC cells (57). Sesamol acts as an antioxidant at lower concentrations, while at higher concentrations it exhibits pro-oxidant effects, which decrease the viability of colon cancer HCT116 cells via interruption of the cell cycle at the S-phase and induces apoptosis via mitochondrial dysfunction (57).

Phenolic acid. Gallic acid is a type of phenolic acid that is present in dietary substances, including blackberries, chocolate, walnuts, raspberries, clove, vinegar, wine, green tea and herbs, including oak, drosera, golden root, stinging nettle and Chinese mahogany (58,113). Gallic acid is associated with oxidative stress and arrests HCT-15 cells at the sub G₁ phase (58). Additionally, gallic acid has been reported to activate p53 upregulated modulator of apoptosis, which is a pro-apoptotic protein that potentiates the release of cytochrome *c* from the mitochondria via disruption of the mitochondrial membrane potential (MMP), which demonstrates the involvement of the intrinsic apoptosis pathway (114).

Hispidin. Hispidin is a phenolic compound isolated from *Phellinus linteus*, a medicinal mushroom that is cultivated in Korea, Japan and China, and is well known for its antioxidant activity (59). Hispidin induces apoptosis and ROS generation in colon cancer cells (59). Additionally, hispidin increases the p53 level and promotes the expression of its downstream

protein Bax, while decreasing the expression of the anti-apoptotic protein Bcl-2, which contributes to the intrinsic apoptosis pathway. Furthermore, increased expression of death receptor 3 and cleavage of caspase-8, caspase-1 and PARP indicates the involvement of the extrinsic pathway in hispidin-induced apoptosis (59).

Hydroxytyrosol (HT). HT is an important phenolic compound present in virgin olive oil (77). HT is transformed into several metabolites, including phenylacetic (PA), phenylpropionic acid (PP), hydroxyphenylpropionic (HPP), dihydroxyphenylpropionic (diHPP) acids and catechol, via phase II metabolism or by intestinal microbials (115-117). HT, PA and HPP exhibit anti-proliferative and pro-apoptotic activities in colon cancer Caco2 and HT-29 cells. Whereas, PP and diHPP are only associated with apoptosis in HT-29 cells (78). HT-induced mitochondrial dysfunction and caspase-3 activation in CRC cells indicates an involvement of the intrinsic apoptosis pathway (78,118).

Resveratrol. Trans-resveratrol, a natural stilbene present in wine and grapes, has been extensively investigated for its anti-inflammatory and anticancer activities (119). It has been reported to inhibit cell proliferation signaling pathways in a number of studies (120-123). In SW-620 and LoVo cells it has been reported to induce apoptosis via the mitochondria-dependent and -independent pathways via an upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins (121,122).

Resveratrol has also been investigated in combination with etoposide in CRC cell lines (120-122). Synergistic effects have been observed on cell growth inhibition via downregulation of mitogen-activated protein kinase signaling pathways and an increase in apoptosis via activation of p53 (124-126). Additionally, a combination of resveratrol and grape seed extract has been reported to suppress Wnt/ β -catenin signaling and increase mitochondria-dependent apoptosis in *in vitro* and *in vivo* models (126).

Cumarins. Clausenidin is a natural pyranocoumarin obtained from *Clausenidin excavate*, which is a wild shrub of the Rutaceae family that is commonly used in Asian folk medicine. Clausenidin induces cell cycle arrest at the G₀/G₁ phase and apoptosis of HT29 cells, which is demonstrated by DNA fragmentation, MMP loss, increased expression of the pro-apoptotic protein Bax, cytochrome *c* release, Apaf-1 gene expression and caspase-9 and caspase-3 activities. ROS generation also serves a role in Clausenidin-induced apoptosis (60). In summary, these events indicate an activation of the mitochondria-mediated intrinsic apoptosis pathway following treatment with Clausenidin.

6. Alkaloids

Piperine. Piperine is an amide alkaloid extracted from the fruits of black and long pepper plants (*Piper nigrum* Linn. and *Piper longum* Linn.) (45). Piperine arrests the cell cycle and inhibits CRC cell proliferation independent of p53 status (45,65). Piperine induces apoptosis by inhibiting the cell survival PI3K/Akt signaling pathway and upregulating

ER stress response proteins, including inositol-requiring enzyme-1 α , CHOP and binding immunoglobulin protein, which results in MMP loss, cytochrome *c* release and PARP cleavage, which indicates a role of the intrinsic pathway in piperine-induced apoptosis (65).

Colchicine. Colchicine is an alkaloid isolated from *Colchicum autumnale* (meadow saffron) or *Gloriosa superba* (glory lily) (127). Colchicine is understood to halt cancer cell growth by its antimetabolic activity (128). In colon cancer HT-29 cells, colchicine induces apoptosis via MMP loss, ROS production, caspase-3 activation, upregulation of pro-apoptotic Bax, downregulation of anti-apoptotic Bcl-2 and phosphorylation of p38, which indicates an involvement of p38-regulated intrinsic apoptosis pathway (61).

Xylopin. Xylopin is an aporphine alkaloid present in the stem of *Xylopi laevigata* (62); however, few studies have investigated this compound. Xylopin has been reported to arrest HCT116 cells at the G₂/M phase and activate ROS-dependent intrinsic apoptosis independent of the p53 pathway (62).

Capsaicin. Capsaicin is a major pungent component in hot red pepper (79). Capsaicin induces apoptosis in colon cancer cells by arresting the cell cycle at the G₀/G₁ phase and is associated with an upregulation of the pro-apoptotic protein Bax in conjunction with PARP cleavage (79,80). Capsaicin alters important cell cycle proteins, including decreasing the expression of cyclin D1 (129) and increasing the expression of p21 (80). Both p21 and Bax are downstream targets of p53 (80). Capsaicin also increases the expression of p53 and decreased apoptosis is observed in p53-knockdown cells, which indicates a key role of p53 in capsaicin-induced apoptosis (80).

Berberine. Berberine is an alkaloid present in numerous medicinal plants, including *Hydrastis canadensis*, *Berberis aristata*, *Coptis chinensis*, *C. rhizome*, *C. japonica*, *phellodendron amurense* and *P. chinense* Schneid, and other plant species used in traditional medicine (130). Berberine is known for its anticancer properties in several types of cancer, such as prostate cancer, neuroblastoma and osteosarcoma (131-133). In colon cancer cells, berberine induces apoptosis via caspase-dependent and -independent mechanisms (130,134,135). In SW480 cells it induces cell cycle arrest at the G₀/G₁ phase and increases the expression of p21 (130). Furthermore, berberine induces the mitochondria-mediated apoptosis pathway by activating apoptosis-associated proteins, including caspase-3 and caspase-9, induces the cleavage of PARP, upregulates the pro-apoptotic protein Bax and downregulates the anti-apoptotic protein Bcl-2 (135). Additionally, the activation of caspase-8 by berberine in SW480 cells functions as a non-apoptotic inhibitor of angiogenesis by decreasing the release of vascular endothelial cell growth factor (135). In HCT-8 cells, berberine arrests the cell cycle at the S phase, and induces apoptosis via activation of the extrinsic and intrinsic apoptosis pathways via an upregulation of Fas, FasL, TNF α , Bax and caspase-3, and a downregulation of Bcl-2 (83,136).

Harmin. Harmin is a β -carboline alkaloid isolated from the seeds of *Peganum harmala* (137). Harmin has traditionally been used in medicinal preparations in the Middle East, Central Asia and South America (137). Harmin inhibits SW680 cell proliferation by arresting the cell cycle at the S and G₂/M phases, and inhibiting Akt and ERK-mediated cell survival pathways (84). Additionally, harmin activates the mitochondria-mediated intrinsic apoptosis pathway via downregulation of the anti-apoptotic proteins Bcl-2, Mcl-1 and Bcl-xl, and upregulation of Bax (84).

7. Evidence from clinical trials

As aforementioned, a number of phytochemical groups have been demonstrated to induce apoptosis of CRC cells via multiple pathways in *in vitro* studies. However, clinical studies have been only performed with a limited number of phytochemicals. A phase I pilot study with resveratrol reported that it downregulates Wnt target gene expression in the normal colonic mucosa of patients with CRC, while it upregulates Wnt target genes, including myc and cyclin D1, in colon cancer (138). The mechanism of this increase remains to be completely elucidated and requires further investigation. The resveratrol-induced downregulation of the Wnt-associated genes in normal colonic mucosa may exert a protective effect as Wnt and its downstream effectors are known to regulate processes involved in tumor initiation, tumor growth and metastasis (139). Another study that investigated the efficacy of resveratrol in patients with colorectal adenocarcinoma demonstrated a 5% reduction in tumor cell proliferation, which indicates that daily oral doses of resveratrol at 0.5 or 1.0 g are sufficient to induce anti-carcinogenic effects (140). However, further clinical evaluation is required before it may be used as an alternative to non-steroidal anti-inflammatory agents and selective cyclooxygenase inhibitors in CRC chemoprevention (140).

Flavonols are understood to inhibit colorectal carcinogenesis via multiple mechanisms, including attenuation of inflammation (141-144). Elevated blood levels of IL-6 have also been observed in colorectal adenoma (145). In a 4-year, randomized, multi-center, nutritional intervention trial study it was demonstrated that a high flavonol intake results in a reduction of serum IL-6 level, which decreases the risk of colorectal adenoma recurrence (146).

An open non-randomized clinical study was performed with curcumin at dose of 4 or 2 g in patients with ≥ 8 aberrant crypt foci (ACF) in a colonoscopic examination. Curcumin at a 4 g daily dose for 30 days reduced ACF by 40%, while a 2 g dose exhibited no effect (147). Another clinical study demonstrated that administration of curcumin increased the body weight of patients with CRC, reduced serum TNF- α levels, upregulated p53 and increased DNA fragmentation in CRC cells (148).

8. Conclusions and future directions

Despite significant progress in the diagnosis and treatment of cancer, the incidence of CRC is increasing worldwide and is expected to rise by 60% by 2030 (1). Mutations or alterations in cancer are a major challenge for effective management. Due to

the high incidence of resistance and adverse effects-associated with chemotherapeutic drugs, there is an urgent requirement to develop more effective therapeutics (149). Phytochemicals are known sources of various compounds that are currently used as chemotherapeutic drugs (36,37). The current review summarized previously published studies regarding the effect of phytochemicals in CRC. To date, an extensive number of studies have been performed to identify molecular pathways involved in CRC and the effects of specific phytochemicals have been examined, primarily in preclinical trials. However, only a limited number have been performed in clinical settings. Therefore, for the majority of phytochemicals it is too early to conclude their anticancer properties. Further extensive research on phytochemicals is required to promote understanding and elucidate their molecular targets, drug interactions, ideal dosages, long-term safety and adverse effects.

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Authors' contributions

KA and SFZ contributed to the planning and design of the study; KA drafted the manuscript; KA, SFZ, ZC, DZ, SAS and HI performed the critical revisions of the manuscript and reviewed the intellectual content.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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