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Revisión / Review

Phytochemicals and colorectal cancer: About polyphenols

[Fitoquímicos y cáncer colorrectal: Acerca de los polifenoles]

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Abstract: Dietary consumption of polyphenols, found in fruits and vegetables, has been associated with a potentially protective role in colorectal cancer (CRC). To establish the state of knowledge regarding advances in polyphenols, CCR and action mechanisms a systematic review and an analysis of information available until 2021 were made. Results indicate that only some polyphenols have *in vitro*, preclinical and clinical studies. These studies showed that polyphenols will inhibit human CRC cell invasion, migration, metastasis formation, tumor growth. Action mechanisms involve signaling pathways that modulate genes, proteins, markers or cell death inductors, like the AMPK pathway, caspases, Bcl-2, p-Akt, and NF-kB, lysosomal and mitochondrial dysfunction, cellular cycle arrest, among the best known and implied in CRC. Overall, *in vitro*, preclinical and clinical data on phytochemicals against CRC are still not sufficient and therefore the preventive or therapeutic impacts of dietary phytochemicals on CRC development deserve further research.

Keywords: Flavonoids; Polyphenolic acids; Action mechanisms; Cellular cycle; Apoptosis

Resumen: El consumo dietético de polifenoles, que se encuentran en frutas y verduras, se ha asociado con un papel potencialmente protector contra el cáncer colorrectal (CCR). Para establecer el estado del conocimiento respecto a los avances en polifenoles, CCR y mecanismos de acción, se realizó una revisión sistemática y un análisis de la información disponible hasta el año 2021. Los resultados indican que sólo algunos polifenoles cuentan con estudios in vitro, preclínicos y clínicos. Estos estudios demostraron que los polifenoles inhiben la invasión, migración, formación de metástasis y crecimiento de tumores de células de CCR humanas. Los mecanismos de acción involucran vías de señalización que modulan genes, proteínas, marcadores o inductores de muerte celular, como la vía AMPK, caspasas, Bcl-2, p-Akt y NF-kB, disfunción lisosomal y mitocondrial, parada del ciclo celular, entre los más conocidos e implicados en el CCR. En general, los datos in vitro, preclínicos y clínicos sobre fitoquímicos contra el CCR aún no son suficientes y, por lo tanto, los impactos preventivos o terapéuticos de los fitoquímicos dietéticos en el desarrollo del CCR requieren más investigación.

Palabras clave: Flavonoides; Ácidos polifenólicos; Mecanismos de acción; Ciclo celular; Apoptosis

ABBREVIATIONS

ACF, aberrant crypt foci; AMPK, AMP-activated mitogen protein kinase; p-AMPK phosphorylate activated protein kinase; Akt, Protein kinase B, AOM, azoxymethane; AP-1, activator protein-1; Bad, Bcl-2- B-cell lymphoma; Bak, Bcl-2 homologous antagonist/killer; Bax, B-cell lymphoma 2 associated X protein; Bcl-2, B-cell lymphoma; Bik, Bcl-2 interacting killer; cdc, cell division cycle; CDK, cyclin-dependent kinase; CSN6: constitutive photomorphogenesis signalosome subunit 6; COX, cyclooxygenase; CRC, colorectal cancer; CXCR4, C-X-C chemokine receptor type 4; DMH, 1,2-dimethylhydrazine; DSS, 4,4-dimethyl-4-silapentane-1-sulfonic acid; EA, ellagic acid; EGCG, epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; Erk 1/2, extracellular- signal-regulated kinase 1/2; FASL, first apoptosis signal ligand, 5-FU, 5-fluorouracil; FLT4, Fms-related tyrosine kinase 4; GA, gallic acid; GSK-3β, glycogen synthase kinase 3-β; HSP-70, heat shock protein 70; IGF-1, insulin-like growth factor; IL, interleukin; IPP, isopentenyl diphosphate; JNK, Jun N-terminal kinase; LTB4, Leukotriene B4; miRNA: Micro-RNAs, MMP, matrix metalloproteinase; mTOR mammalian target of rapamycin. c-MYC, Myc proto-oncogen; NF-κB, nuclear factor kappa B; Notch1, Neurogenic locus notch homolog protein 1, PARP, poly (ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; RXRα, retinoid X receptor alpha; SIRT1, sirtuin 1; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor alpha; Wnt, wingless-type; XIAP, X-linked inhibitor of apoptosis protein

INTRODUCTION

Colorectal cancer (CRC) continues being one of the principal causes of morbidity and mortality globally. The GLOBOCAN 2020 report describes that the estimated CRC burden has had an important increase over the years, now being the second-most-lethal cancer, after lung cancer; for the same publication, CRC continues being the third most-diagnosed malignant neoplasm throughout the world (Globocan 2022).

However, CRC is one of the most preventable forms of cancer because it is associated with modifiable risk factors, like obesity, sedentarism, alcohol consumption, intake of red and processed meats, and low consumption of fruits and vegetables (Zhou & Rifkin, 2021).

Regarding the intake of fruits and vegetables for cancer prevention, it is known that compounds synthesized by plants, such as bioactive secondary metabolites, which play a role in their growth or in their defense against competitors, pathogens or predators, are not only responsible for their color, flavor, but for many pharmacological activities (Choudhari *et al*., 2020). Over 12,000 Phytochemicals (FC) have been identified, among them polyphenol compounds of interest in CRC prevention and treatment.

The polyphenol group is divided into four chemical types: i) flavonoids that represent 60% of polyphenols and include quercetin, kaempferol, catechins and anthocyanins; ii) phenolic acids, for example stilbenes and lignans, make up approximately 30%; iii) phenol amides; and iv) others without chemical category, like resveratrol.

These compounds have been found in fruits, vegetables, whole grains, legumes and nuts; among fruits, berries, plums, cherries, and apples are the richest in polyphenols (Afrin *et al*., 2020). Among vegetables, the highest levels of polyphenols are found in broad beans, olives, onions, and spinach (Choudhari, *et al*., 2020; Afrin *et al*., 2020).

Polyphenols, specially flavonoids, are powerful antioxidants (Zhang *et al*., 2015b; Choudhari *et al*. 2020), therefore, they have been used in numerous epidemiological and experimental studies to evaluate their possible beneficial effects in multiple disorders, thus, *in vitro* and *in vivo* studies have demonstrated that these compounds may exert anti-inflammatory, immunomodulatory, and anticancer effects (Choudhari *et al*., 2020). Action mechanisms of phytochemicals in these biological activities have not been established, but it is known that many of them can interfere in cell functions, altering activation of transcription factors that regulate gene expression and modulate cell metabolism (Afrin *et al*., 2020; Choudhari *et al*., 2020); likewise, these prevent the appearance of tumors, cell proliferation, invasion and metastasis of many types of cancer, among them CRC; however, the biological activity of many of these compounds is partly unknown (Afrin *et al*., 2020; Choudhari *et al*., 2020), especially in colorectal cancer.

Hence, this review focused on describing the

action mechanisms and effects of some polyphenols present in fruits and vegetables from the diet against colorectal cancer.

Literature review

This bibliographic review adopted the approach by the declaration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) and seeks to show the antitumor potential in CRC of some polyphenols, specially flavonoids and polyphenolic acids present in common foods.

The keywords used in the databases (Google Scholar, PubMed, SciELO, Science Direct, Springer), until November 2021, were: colorectal cancer and phytochemicals, phytochemicals and/or action mechanisms and CRC cancer. Only selecting studies between 2009 and 2021 that described phytochemicals and their action mechanisms over cell models, animals, preclinical and clinical studies of colorectal cancer. After this search, flavonoids and polyphenolic acids mentioned in three or more of these studies, which also described action mechanisms and the type of study (*in vitro*, clinical, and preclinical) were included as keywords in the search. The principal phytochemicals fulfilling this characteristic were: quercetin and its derivates, anthocyanin extracts, proanthocyanins, genistein and its derivates, epigallocatechin-3-gallate (EGCG), Kaempferol, caffeic acid and its derivates, resveratrol and its metabolites, Gallic acid, curcumin and its derivates.

Initially, titles and abstracts were reviewed, then, full articles and, finally, the relevance of each work was analyzed according to the objective of this review. In all, 80 articles were reviewed of which 60 complied with the inclusion criteria, however, several articles citing them and with relevance for the review were also reviewed.

Polyphenols and colorectal cancer

Polyphenols may be classified according to their chemical structure, function or signaling pathway through which they act. Regarding their chemical structure, they can be classified as: phenolic acids, flavonoids, stilbenes, coumarins and tannins, (Afrin *et al*., 2020).

Several studies have investigated the anticancer effects of dietary phytochemicals in CRC models (Afrin *et al.*, 2020) and in humans (Pintova *et al*., 2019), given that it is known that from 70% to 90% of CRC is correlated with dietary factors, and optimization of the diet could avoid most of the cases; studies have revealed that polyphenols can modulate cell proliferation, regulate the cellular cycle, participate in multiple signaling pathways that often interrupt tumor initiation, proliferation and propagation. Also, evidence indicates their participation in decreasing the number and size of polyps, tumor size and oxidative stress markers (Carroll *et al*., 2011; Zhang *et al.*, 2013; Afrin *et al*., 2020).

Several of these phytochemicals are found in *in-vitro*, preclinical and/or clinical trial phase, with some conclusive results at pharmacological level due to their effects and selectivity of the therapeutic targets and lesser collateral effects than synthetic compounds (Zhang *et al.*, 2013; Carroll *et al*., 2011).

Action mechanisms of polyphenols on colorectal cancer

Polyphenols are compounds with great antioxidant potential, found in common vegetable products in our diet, like fruits (grapes and its derivates, lemon, cherry, apple), vegetables (soy, leeks, red cabbage, broccoli, onions, radish, beet, Tea (green and black). This bibliographic review included *in-vitro*, preclinical and clinical studies for flavonoid-type polyphenols, like quercetin, anthocyanins, genistein, epigallocatechin-3-galacto, Kaempferol and Gallic acid, resveratrol and curcumin polyphenols.

In-vitro studies in colorectal cancer cells

The following describe *in-vitro* studies for each of the polyphenols mentioned in colorectal cancer cell models and the action mechanisms shown.

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavanol present in high concentrations as o – glycosides or aglycones, in which one or more sugar groups are joined to phenolic groups through glycosidic bonds. It is common in fruits and vegetables, specially onion, broccoli, apple, tea, red wine, and capers (Afrin *et al*., 2020).

Quercetin plays an important role in inhibiting tumorigenesis in colon cells (DLD-1, HT-29, and HCT-116) through antioxidant, anti-inflammatory, antiproliferative actions, and proapoptotic mechanisms.

Proapoptotic effects

Many studies on several CRC cell models have addressed the proapoptotic effect of quercetin, highlighting actions like diminished expression of B-cell lymphoma (Bcl-2), lymphoma extra-large B cells (Bcl-xl), which are proliferation cell markers; said studies have also evidenced inhibition of factors controlling transcription and repair of cell DNA, like the Nuclear factor kappa B (NF-kB).

Moreover, this flavonoid stimulates the signaling pathways dependent on mitogen-activated protein kinases (MAPK), which – in turn – regulate other subfamilies of signaling pathways dependent on MAPK, like p38, JNK, and ERK, apoptosis-inducing factors (Zhang *et al*., 2015a; Kee *et al*., 2016; Yang *et al*., 2016). At the same time, quercetin improved expression of tumor suppressor genes, like p53, increased caspases 3, 7, 8 and 9, central proteins in programmed cell death (Refolo *et al*., 2015; Zhang *et al*., 2015a; Kee *et al*., 2016; Yang *et al*., 2016).

Effects on the cellular cycle

The studies reviewed show that quercetin or its derivates suppressed progression of the cellular cycle by blocking it in the G0/G1 phase (Yang *et al*., 2016) and the G2/M phase (Zhao *et al*., 2017).

Anti-inflammatory effect

On the anti-inflammatory effects de la quercetin, it was found that in Caco-2 cells, it suppresses expression of the toll-like receptor (TLR), the NF-κB, and pro-inflammatory factors, like IL-6, COX-2 and TNF-α, NF-κB (Han *et al*., 2016). In DLD-1, Caco-2, HT-29 cell models, it suppressed the Wnt/β-catenin and Akt-CSN6-MYC pathways (Refolo *et al*., 2015; Yang *et al*., 2016), implied in the malignant start, progression, and transformation of cells through generation of reactive species. Table No. 1 summarizes the actions of quercetin on cell models.

Table No. 1
***In-vitro* activity and action mechanisms of flavonoids and polyphenolic acids on colorectal cancer**

Phytochemical	Dose, duration and model	Actions	Molecular Effects	Reference
Quercetin	25-200 μM; 48 h; HT-29	Inhibits cell proliferation, arrests cell cycle, induces apoptosis.	↓ p-Akt, MYC, At phase G0/G1, Bcl-2, ↑Bax, p53, caspase 3	Yang *et al*., 2016
	10-100 μM; 24-48 h; CT-26	Induces apoptosis	↑ c.PARP, caspases 3-9,↓Bcl-2, Bcl-xl	Kee *et al*., 2016
	25-100 μM; 24 h, Caco-2, SW-620	Induces apoptosis	↑ Bax, caspases 3-9, ↓Bcl-2, NF-kB	Zhang *et al*., 2015a
	25-200 μM; 24 h, HT-29, HCT-15	Inhibits cell proliferation, induces apoptosis	↓p-Akt, p-GSK3β, Cyclin D1, ↑COX-2 ROS dependent, ↑ caspase 3, cyto-c	Raja *et al*., 2017
Quercetin derivatives	25-200 μM; 24 h, HCT-116	Induces oxidative stress and apoptosis	↑ ROS, ↑ IRE1-α, XBP-1, ion Ca^{+2}, ↓ MMP, ↑ p-JNK, Bax, cyto-c, caspase 3-9, ↓ Bcl-2	Khan *et al*., 2016
Extracts and metabolites of Anthocyanin and Proanthocyanidins	15 μM; 24 h, SW-620, HCT-116	Arrests cell cycle, induces autophagy	At phase G2/M, ↑LC-I/II, Beclin, SQSTM1/p62, ↑Atg7, pErk1/2, p-JNK, p-p38 MAPK, ↑	Zhao *et al*., 2017a
	0.25-10 mg/ml; 24 h, HCT-116; HT29	Induce apoptosis, Arrests cell cycle	↓Survivin, cIAP-2 y XIAP, phase A1/G1	Mazewski *et al*., 2018
	1-20 μg/ml; 24 h, HT-29	Inhibits cell proliferation, decreases inflammation	↑ ROS, ↓ TNF-α, IL1β y NF-k β	Venancio *et al*., 2017

	100-150 µmol/l; 48 h, HP-29	Induce apoptosis	↑ Caspase 3	López de las Hazas *et al*., 2016
	10-80 µg/ml; 48 h, SW480; SW620	Induce apoptosis	↑ Caspasa-8, p-p38MAPK	Minker *et al*., 2015
Genistein	30-70 µM; 48 h; HT-29	Inhibits cell proliferation, induces apoptosis, suppresses migration and invasion	↓ p-p38, MAPK, ↑ caspase -3, ↓ MMP2	Shafiee *et al*., 2016
	0-100 µmol/l; 2 h; IICT-116	Induces apoptosis, arrests cell cycle	↓MMP, ↑ROS, At phase G2/M	Wu *et al*., 2017
Genistein derivatives	5-20 µM; 12-24 h; HCT-116, HT-29	inflammation decreases	↓ NF-kβ/p65, TNF-α, IL-6, IL-1β	Du *et al*., 2016
	1-100 µM; 24 h, HCT-116	Inhibits cell proliferation, stops cell cycle, decreases inflammation	↓PCNA, BcL2, cyclin D1, At phase G0/G1, ↓ NF-kβ, p-IkB, IKKα/β	Wang *et al*., 2016a
Epigalocatequin-3-galate (EGCG)	50-150 µM; 48-72 h; IIT-29, IICT-116, SW-480	Induces epigenetic modification	↓RXR-α, β-Catenin, Cyclin D	Morris *et al*., 2016
Kaempferol	60 µmol/l; 24 h, HT-29	Inhibits cell proliferation, induces apoptosis	↓IGF-IR, ErbB3, p-PI3K/Akt, p-Erk/12	Lee *et al*., 2014a
	60 µmol/l, 24-48 h, HT-29, SW-480	Induces apoptosis	↑caspase-3,7,9, PARP, Bik, Bad, ↓ Bcl-xl, ↑ FasL, cyto-c	Lee *et al*., 2014b
Gallic acid	70 µmol/l; 24-72 h, HCT-15	Induces apoptosis	↑ROS, ↓ MMP	Subramanian *et al*., 2016
	40 µg/ml; 2-6 días, HTC-116	Inhibits cell proliferation	↓ CSC marker	Lee *et al*., 2016
Caffeic acid and derivatives	10-80 µM; 48 h, HCT-116; HT-29	Induces apoptosis	↑p53, caspasa-3, Bax, P38mapk, cyto-c	Tang *et al*., 2017
Resveratrol	1-10 µM; 14 días, HCT-116 y SW-480	Inhibits cell proliferation	↓NF-kB, ↑ Sirt1	Buhrmann *et al*., 2016
			↓Ras, Raf, MEK Erk1/2, ↑Bak1, Bok, Bik, Noxa, Bad Bax, p53, Apaf1	
	1-100 µmol; 24-72 h, SW-620	Inhibits cell proliferation, induces apoptosis	↓Bcl-2, Bcl-xl, Bag1, ↑caspases 3-7-9	Chen *et al*., 2016
	20-40 µM; 24-48h, LoVo	Inhibits cell proliferation	↑ PCNA, p38MAPK	Yuan *et al*., 2016
	1-100 µM; 48 h, HT-29	Induces epigenetic modification.	↑ Histone levels and gH2AX	San Hipolito-Luengo *et al*., 2017
Resveratrol Metabolites	20-40 µM; 24-48 h, HCT-116; HT-29	Inhibits cell proliferation, induces apoptosis, arrests cell cycle	↑ p-53, Bax, caspase-3, PARP, At phase S, ↑p21, ↓ Cyclin E, p-Rb	Sun *et al*., 2016
Curcumin and analogues	30 µM; 4 h, HCT-116	Inhibits cell proliferation, induces autophagia	↓ EIF2, elF4/p70S6K, p-mTOR, ↑ Autophagosomes, ↑ Lamp1, Hsp70	Wang *et al*., 2016b
	200 µM; 1 h, SW-	Inhibits cell proliferation	↓ mTORC1, ↑p-Erk1/2,	Sato *et al*., 2017

620 y SW-480		p-AMPKα1, ↓ p-MEK	
10-40 μmol/l; 24 h, SW-620	Inhibits cell proliferation, Suppresses EMT	↓Wnt, B-catenin, TCF4, ↑ Axin, ↑NKD2, E-cadherin, ↓ Vimentin, CXCR4,	Zhang *et al*., 2016b
5-20 μM; 12-24 h, HCT-116	Induce autophagia	↑ TFEB lysosomal pathway	Zhang *et al*., 2016a
10 μM; 24 h, SW-480; LoVo	suppress the invasion	↑ AMPK, ↓p65 NF-kB, uPA, MMP-9	Tong *et al*., 2016
12.5 μM; 48 h, HCT-116	Induces epigenetic modification.	↑ miR-491, ↓ PEG10, Wnt/β-catenin	Li *et al*., 2018

Anthocyanins

Anthocyanins are water-soluble pigments found in the vacuoles of plant cells and give the red, purple or blue color to leaves, flowers and fruits; these are abundant on the skin of red grapes; are classified among flavonoids and their function in plants is to attract predators to consume their fruits and help disperse the seeds of the fruit for the reproduction of the species (Afrin *et al*., 2020).

***In-vitro* studies**

Anthocyanins induce chemo-preventive effects, including anti-inflammatory, antiproliferative effects, with induction of apoptosis, regulation of the cellular cycle, anti-invasion activities, and anti-angiogenesis.

Apoptotic effects

Anthocyanins and extracts rich in anthocyanidins induce in COLO 320DM cells, apoptotic death by increasing the c-PARP, caspase-3 and Bax/Bcl2 ratio (Hsu *et al*., 2012). In HT-29 cells, they induce the decrease of the Survivin inhibitor, linked to the X chromosome apoptosis protein (XIAP) (Mazewski *et al*., 2018); in this same cell line, anthocyanins suppressed cell growth by inhibiting pro-oncogenic signals, like AP-1, NF-kB and STAT-1 activity. In HT-29 cells, after treatment with extracts rich in anthocyanins, increased caspase-3 was noted (López de las Hazas *et al*., 2016).

Effects on the cellular cycle

Anthocyanin extracts on COLO-320DM and HT-29 cells detained the cellular cycle in the G0/G1 phase (Hsu *et al*., 2012); in Caco-2 cell lines, these blocked the cellular cycle in the G0/G1 phase (Forester *et al*., 2014).

Anti-inflammatory effects

Anthocyanin extracts suppress proliferation of HT-29 cells by increasing generation of reactive oxygen species (ROS), also exerting anti-inflammatory effects by suppressing expression of NF-κB1, TNF-α, IL-6, and IL-1β inflammation markers (Venancio *et al*., 2017., Afrin *et al*., 2020).

Genistein

Genistein is an isoflavone present in foods, like soy, common hop or red clover. Isoflavones are a group of plant chemical substances included among phenolic compounds. Genistein is the aglycone free form of genistein (glycosylated form) (Afrin *et al*., 2020)

Genistein has attracted much attention due to its effects and probable anticancer efficacy with function in several CRC signaling pathways.

Proapoptotic effect

The chemo-preventive and proapoptotic activity of genistein has been demonstrated through inhibition of the Wnt/β-catenin signaling pathway (Du *et al*., 2016; Sekar *et al*., 2016); EGFR and p38 MAPK (Shafiee *et al*., 2016) and NF-κB, as well as Bcl-2 (Wang *et al*., 2016b), decreased expression of p-GSK-3β levels (Du *et al*., 2016) and β-catenin target genes, including the proliferating cell nuclear antigen (PCNA), cyclin D1 and c-MYC (Du *et al*., 2016; Wang *et al*., 2016a).

Effect on the cellular cycle

Genistein suppressed cell growth by blocking the G0/G1 phase (Du *et al*., 2016; Wang *et al*., 2016b)

and G2/M phase (Wu *et al*., 2017).

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is produced through naringenin-chalcone-naringenin; its principal source is green tea, traces are also found in skins of apples, plums, onions, hazelnuts, nuts (Afrin *et al*., 2020).

Proapoptotic effects

It has been reported that EGCG exerts anticancer effects against different CRC cell line models modulating multiple signaling pathways. In these cells, EGCG inhibited cell proliferation by suppressing Wnt/β-catenin and PI3K/Akt (Kumazaki *et al*., 2013) signaling pathways and inducing apoptosis through activation of p53-dependent and p53-independent pathways (Afrin *et al*., 2020). In colon cancer cells with APC mutation, EGCG suppressed cancer cell growth through inhibition of Wnt/β-catenin stimulating β-catenin phosphorylation and proteasomal degradation through an independent system of GSK-3β and protein phosphatase 2A and repressing cyclin D1 and expression of c-MYC (Oh *et al*., 2014).

In HT-29 cells and HCT-116, EGCG and its derivates reduce expression of the RXRα gene, important for dimerization with other nuclear transcription factors (Morris *et al*., 2016; Toden *et al*., 2016); thus, EGCG suppressed Notch1, Bmi1, Suz12 and Ezh2, and miRNA self-renewal suppressors and upregulated, miR-34a, miR-145 and miR-200c, which are some of the key pathways targeted in 5FU-responsive CRC cells. Regarding this last effect, the same authors investigated the Chemo-sensitizing effects of EGCG on 5-fluorouracil-resistant CRC cells and spheroid-derived cancer stem cells, reporting that EGCG ameliorated 5FU-induced cytotoxicity and inhibited proliferation in 5FU-resistant cell lines through intensification of apoptosis and arrest of the cellular cycle.

Kaempferol

Kaempferol is a flavonoid aglycone found mainly in beans, bee pollen, broccoli, cabbage, capers, cauliflower, chia seeds, chives, cumin, moringa leaves, endive, fennel, garlic and in fruits, like apples, grapes, abundant in black currants (Imran *et al*., 2019).

Proapoptotic effects

Studies have demonstrated in *in-vitro* CRC cell models that kaempferol exerts chemo-preventive effects by suppressing cell growth, inducing apoptosis, and halting the cycle by diminishing the expression of the PI3K/Akt and Erk1/2 pathways of Bcl-xL protein levels (Lee *et al*., 2014b), inhibiting IGF-IR and ErbB3 signaling (Lee *et al*.,2014a; Afrin *et al*., 2020), increase of the membrane-bound first apoptosis signal ligand (FASL), of concentrations of the c-cytosolic and mitochondrial cytochrome, membrane permeability, and Bik and Bad levels (Lee *et al*., 2014b). Kaempferol also blocked ROS production and modulated expression of MAPK, JAK/STAT3, PI3K/AKT, histone H2AX, phospho-p38, p21, p53, cytochrome C release, ERK-1/2 and NF-B. It also suppressed retinoblastoma protein phosphorylation and improved PARP cleavage (Cho & Park, 2013; Imran *et al*., 2019; Afrin *et al*., 2020).

Effects on the cellular cycle

Kaempferol significantly reduced insulin-like growth factor (IGF)-II, the expression of cyclin kinases CDK2, CDK4, phosphatases Cdc25C, Cdc2, cyclins B1, D1, E, A and connexin 43, caspase 3, 7, 8 and 9 activation, as well as PARP activity.

Gallic acid

Gallic acid (3,4,5-trihydroxybenzoic) is a polyphenol found in clove buds, green tea, red fruits, like strawberries, raspberries, blueberries, black tea, red wines and nuts. Gallic acid is found in its free form and as part of tannins (hydrolysable tannins). Gallic acid salts and esters are called gallates (Afrin *et al*., 2020).

Proapoptotic effects

Gallic acid inhibits cell proliferation and the survival rate because it produces inhibition of AP-1, NFkB, and STAT1 transcription factors, besides suppressing Wnt/β-catenin signaling in HCT-116 cells (Lee *et al*., 2016). In Caco cells, it induces apoptosis by activating caspase 2 and 3 expression, increasing ROS generation, and diminishing MMP (Subramanian *et al*., 2016). In addition, in HCT-116 cancer cells, Gallic acid induced differentiation of stem cell cancer cells (CSC) and self-renewal capacity through regulation to low expression of

CSC, CD133, CD44, DLK1 and Notch1 markers (Lee *et al*., 2016; Afrin *et al*., 2020).

Effect on the cellular cycle

In Caco cells, it halts the cellular cycle in the G0/G1 phase by diminishing cyclin D1 levels, (Subramanian *et al*., 2016).

Caffeic acid

Caffeic acid (3-(3,4-dihydroxyphenyl)-acrylic acid) is an organic compound classified within catechols and phenylpropanoids. This yellow solid contains phenolic and acrylic functional groups. It is found in all plants, given that it is a key intermediary in lignin biosynthesis, one of the principal forms of biomass. Coffee is the main dietary source of caffeic acid (CA), besides apples, red wine, green tea, apricots, and prunes with moderate levels of CA (Afrin *et al*., 2020).

Proapoptotic effects

In HCT-116, SW-480, and HT-29 cell lines, caffeic acid phenethyl esters (CAPE) and caffeic acid phenyl propyl esters (CAPPE) suppress cell proliferation by downregulating expression of the p-Akt, mTOR, Erk1/2 and NF-KB, AMPK and p38MAPK signaling cascade and Bcl-2 expression and increasing p53, Bax, caspase-3 and expression of cytochrome c (Tang *et al*., 2017).

Effect on the cellular cycle

In HCT-116, HT-29, and SW-480 colon cancer cells, CA, CAPE, and CAPPE detained the cellular cycle in the G0/G1 phase, suppressing the expression of CDK2, CDK4, cyclin D1, cyclin E, proteins c- MYC, PCNA and increasing the expression of p21cip1/waf1 and proteins p27kip1 (Chiang *et al*., 2014; Tang *et al*., 2017).

Moreover, in the same cell models, decyl caffeic acid (DC), a new derivate of CA, inhibits cell growth by detaining the cellular cycle in the S phase, also inhibiting expression of cellular cycle regulators, which include proteins cyclin E and cyclin A.

Resveratrol

Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a phytoalexin from the family of natural flavonoids produced in plants as a response to an injury caused by bacterial or fungal aggression. The dietary sources of resveratrol include skins of grapes, blueberries, raspberries, and blackberries (Afrin *et al*., 2020).

Resveratrol has a wide range of beneficial effects on human health, including CRC prevention. Several studies have shown the anticancer effects of resveratrol in CRC cell and animal models.

Proapoptotic effect

In cells, it has been found to modulate significantly oncogenic effects by inhibiting proliferation through suppressing the proliferation marker (Ki-67) and various signaling pathways that include NF-KB (Buhrmann *et al*., 2016), Ras, Raf, MEK, Erk1/2 (Chen *et al*., 2016), as well as increase of PCNA (Yuan *et al*., 2016), SIRT1 expression, and modulation of adhesion molecules (Buhrmann *et al*., 2016). Resveratrol also increased expression of the bone morphogenetic protein 9, activating p38 MAPK to induce antiproliferative effects in LoVo colon cancer cells (Yuan *et al*., 2016).

Anti-inflammatory effects

Resveratrol induces anti-inflammatory effects by suppressing PGE2 and COX-2 expression, reducing the levels of PGE2, EP1, EP3, and EP4 receptors in *in-vitro* and *in-vivo* colon cancer models (Feng *et al*., 2016). In SW-620 and LoVo cells, it has been demonstrated that resveratrol-induced apoptosis is produced by the activation of the mitochondrial pathway by upregulating the expression of the pro-apoptotic proteins Bok, Bak1, Bik, Bad, Noxa, Bax, Apaf1 and p53 and downregulating expression of anti-apoptotic proteins Bcl-xL, Bcl-2 and Bag1 (Chen *et al*., 2016; Yuan *et al*., 2016; Feng *et al*., 2016); furthermore, in SW-620, Caco-2, and HCT-116 cells, it increases the cleaved form of PARP, caspase 3, 7 and 9 (Chen *et al*., 2016).

Effect on the cellular cycle

A resveratrol metabolite, pterostilbene, significantly altered the main signaling pathways related to cell propagation, cellular cycle and apoptosis by increasing p53, Bax, c-caspase-3 and c-PARP, and p21cip1/waf1 expression, besides diminishing expression levels of cyclin E and p-Rb in HT-29 and HCT-116 colon cancer cells (Sun *et al*., 2016).

Curcumin

Curcumin is a polyphenol obtained from the rhizome of the *Curcuma longa* plant. It is a diarylheptanoid belonging to the curcuminoid group, phenols of

natural origin responsible for the intense yellow coloring characteristic of this product. Curcumin can modulate several growth factors and signaling pathways responsible for the onset, proliferation, and progression of CRC.

Apoptotic effects

In colon cancer cell cultures, curcumin or its analogues inhibit cell proliferation or survival rate by modulating several signaling pathways, like PI3k/Akt/mTOR, Wnt/β-catenin, GSK-3β kinase (Wang *et al*., 2016a; Montgomery *et al*., 2016; Sato *et al*., 2017; Sufí *et al*., 2017), as well as increased expression of signaling with p-Erk1/2 and p-AMPK (Sato *et al*., 2017). Also, treatment with this flavonoid induces activation of autophagy by inducing mitochondrial and lysosomal dysfunction, through the upregulation of TFEB, Lamp1, Atp6v1a, Uvrag, Atg9b, and LC3y, expression of Lamp1 protein and heat shock proteins 70 (HSP70) (Wang *et al*., 2016b) and stimulates apoptosis by activating caspases, c-PARP, Bax/Bcl-2 ratio, ROS and JNK-mediated activation, as well reduction of MMP and transcription factors Sp1, Survivin and expression of NF-κB, highlighting improved therapeutic effects (Montgomery *et al*., 2016; Sufí *et al*., 2017).

In LoVo and SW-480 cells, the anti-invasive efficacy of curcumin was also associated with AMPK activation and the consequential inhibition of p65-NF-κB, uPA, and MMP-9 (Tong *et al*., 2016) and diminished β-catenin, vimentine, and CXCR4 (Zhang *et al*., 2016a).

Similar results were obtained with six curcumin analogues, which suppressed EGFR expression and tyrosine phosphorylation, increased p53, cytochrome c, caspase 3, 7, 9, c-PARP activated, Bax/Bcl-2 and ROS, and diminished MMP (Montgomery *et al*., 2016; Sufi *et al*., 2017).

Effect on the cellular cycle

Using the SW480, SW620, CT-26, HCT-116, and HT-29 cell lines, curcumin and its analogues halted the cellular cycle phases in G0/G1 and G2/M, through signaling directed to protein control, like p21waf-1/cip-1, cyclin D1, cyclin B1, and cdc2 (Montgomery *et al*., 2016; Sufi *et al*., 2017). Table No. 1 summarizes the *in-vitro* actions of these flavonoids and polyphenolic acids described herein.

In-vitro studies with the polyphenols described indicate overall that they act on cell models in small doses (10 and 200 Mm) and between 24 and 48 h; their action mechanisms involve signaling pathways that modulate genes, proteins, antiproliferative metabolic pathway markers or which induce cell death, like the AMPK pathway and their kinase/phosphatase families, caspases 3, 7, 8 and 9, and p53, among the best known and implied in CRC. Also, these polyphenols achieve inhibition of cell proliferation factors, like Bcl-2, p-Akt, and NF-kB, modulation of kinase pathways (PI3K, AKT, and P-AKT), lysosomal and mitochondrial dysfunction, or detention of the cellular cycle in some of its phases to impede proliferation and promote cell death. Figures 1 and 2 summarize these effects and mechanisms in apoptosis, cellular cycle, DNA repair, inflammation, cell proliferation and maintenance for the flavonoids genistein anthocyanins, Kaempferol, EGCG and some of their dietary sources promising *in-vitro* results gave way to preclinical studies (Table No. 2) in animal models of colorectal cancer; these models are induced by several chemical methods, like azoxymethane (AOM) and dimethylhydrazine (DMH), or with injection of tumors or cancer cell lines (Xenografts). Evidence from *in-vitro* studies also permitted clinical studies (Table No. 3).

In-vivo studies on animal models and humans

Quercetin

Multiple studies exist on mice and rats with DMH-induced CRC that show the effectiveness of quercetin to reduce various symptoms and signs of this type of cancer, thus, a study treating mice with CRC with 50 mg/kg of quercetin, once per week, for five weeks, demonstrated reduction in oxidative stress markers in colon tissue and a decrease in plasma levels of carcinoembryonic antigen (Saleem *et al* 2015), while in a colon cancer xenograft model in mice induced by cancer cell implantation, treatment with quercetin reduced the tumor volume and increased the survival rate (Hashemzaei *et al*., 2017).

According to studies on humans, treatment with quercetin produced a reduction on the abundance of proteobacteria, which are commonly present during intestinal inflammation in patients with colitis (Mukhopadhya *et al*., 2012). Similar results were obtained in randomized dietary intervention study in patients with CRC, which examined the effectiveness of efficacy of a diet low in fat, high in fiber, rich in fruits and high in vegetables that included high intake of flavonols,

including quercetin, on the adenoma recurrence; the results showed significant decrease in the risk of advanced adenoma recurrence, without association between quercetin alone and adenoma recurrence (Bobe *et al*., 2008).

In spite of this last result, the dietary source of quercetin alone is important, given that a study of cases and controls in 2664 patients revealed that increased intake of quercetin was associated with a small reduction in the risk of proximal colon cancer, but not distal colon, and this effect was noted only with a high intake of fruits, but low in tea (Djuric *et al*., 2012).

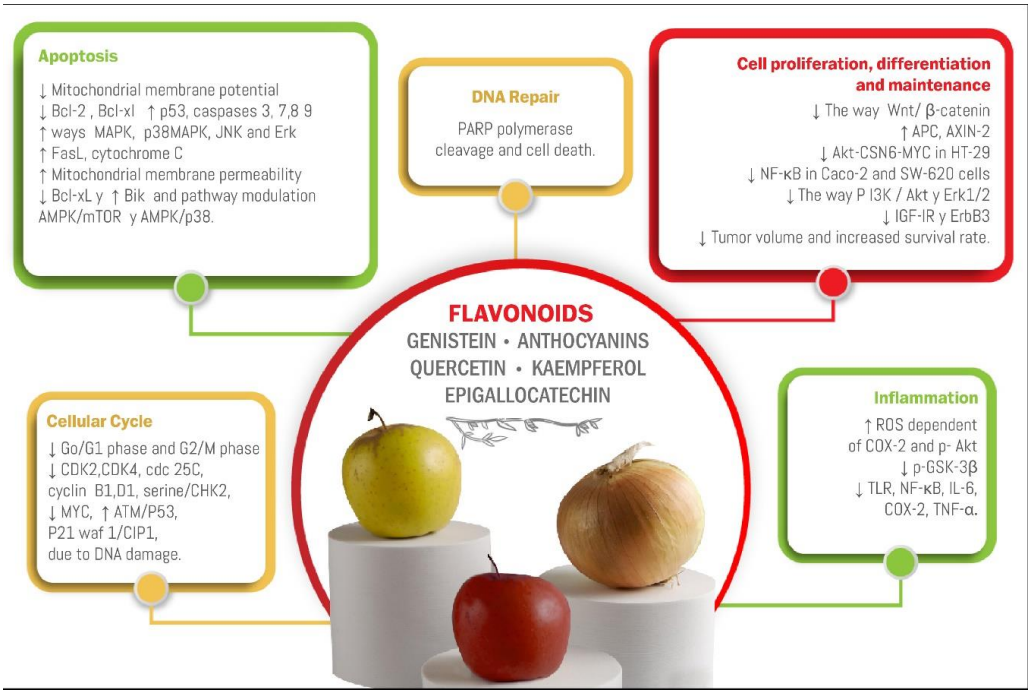

Figure No. 1
Summary of the mechanisms of action in colorectal cancer cell lines of polyphenols of the flavonoids type. Source authors

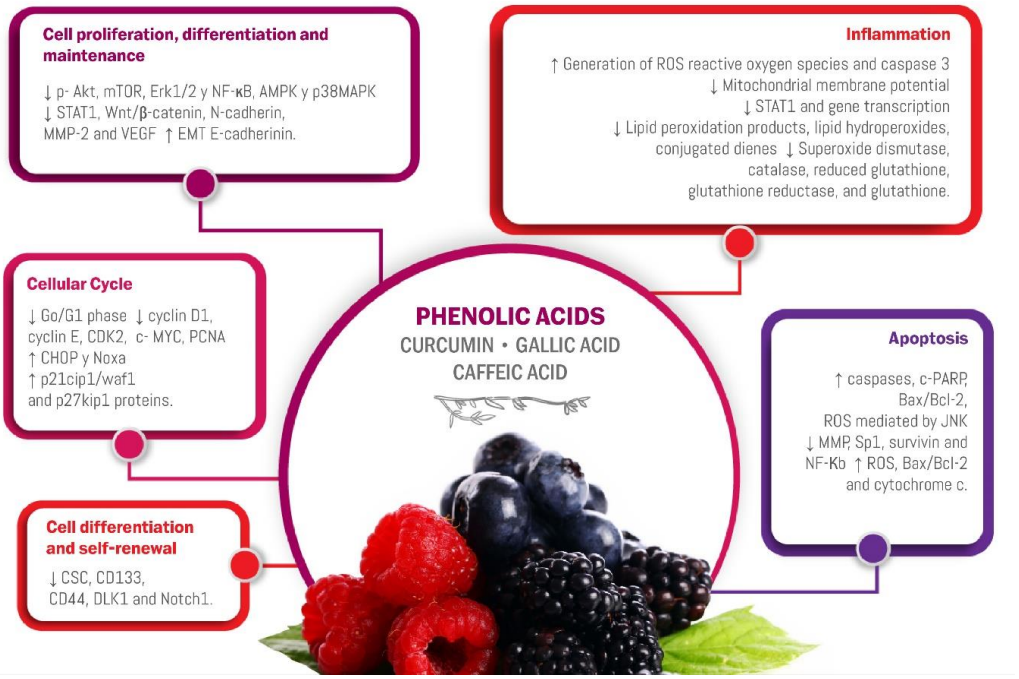

Figure No. 2
Summary of the mechanisms of action in colorectal cancer cell lines of polyphenols of the phenolic acid type. Source authors

Anthocyanin

In relation with studies in animals, for this flavonoid in an AOM-induced mouse CRC model, anthocyanins inhibit the formation and growth of this cancer by reducing inflammation (Lippert *et al.*, 2017). A study on a similar model in mice with AOM-induced CRC and water containing dextran sodium sulfate (DSS) (AOM/DSS model), treatment with extract rich in anthocyanins at 10% reduced the number of tumors (Piberger *et al.*, 2011).

A study, also in animal models, found that at molecular level these induce apoptosis (increasing Bax and cytochrome c), altering the signaling Wnt, suppressing β-catenin and its subsequent proteins expressing c-MYC and cyclin D1 (Charepalli *et al.*, 2015).

Another study using ApcMin mice as genetic model of adenomatous polyposis in humans, mice were fed with a mix of black raspberry anthocyanins (>90% purity), containing mainly cyanidin-3-glucoside isolate (C3G) and mirtoselect (0.03%, 0.1%, or 0.3%) in the diet during 12 weeks, showed that intake of these compounds reduced adenoma burden in function of dose. With the highest doses of the two compounds, the number of adenomas diminished by 45% ($p<0.001$) or 30% ($p<0.05$), respectively, compared with controls (Cooke *et al.*, 2006).

Research on the intake of anthocyanins in patients with CRC have also been promising, for example, in colon biopsies of patients with inflammatory bowel disease, intake of blueberry extracts rich in anthocyanins ameliorated colitis and was associated with reduced NFkB activation and production of pro-inflammatory mediators (Biedermann *et al.*, 2013). Another study in 25 patients with CRC who received myrtocyanin (extract rich in blueberry anthocyanins) in concentrations of 1.4, 2.8, or 5.6 grams (0.5-2.0 grams of anthocyanins) daily for seven days before tumor resection surgery, showed reduced cell proliferation in the biopsies of the tumors extracted (Thomasset *et al.*, 2009).

Similar results were obtained in a study of biopsies of tumors and normal adjacent tissue of patients with CRC who consumed black raspberry powder before tumor resection; the results show

changes in the Methylation status of several promoters of tumor suppressor genes, increased apoptosis and diminished cell proliferation markers (Wang *et al*., 2011).

Genistein

Studies of this flavonoid in animal models show its benefits to combat CRC, thus, an *in-vivo* study using AOM as chemical inducer of colon cancer in male Sprague-Dawley rats showed that rats fed 140 mg genistein/kg body weight since gestation until 13 weeks of age showed downregulation of Wnt/β-catenin and reduction in the total number of aberrant crypts (Zhang *et al*., 2013). Likewise, genistein inhibits AOM/DSS-induced colon cancer by regulating the accumulation of lipid droplets and the SIRT1/FOXO3a pathway in female mice fed with a diet rich in fats containing 250 ppm of genistein for 52 weeks (Qi *et al*., 2019).

Xiao *et al*. (2015), in an orthotopic implantation model of human CRC cells in mice, demonstrated that oral genistein did not inhibit tumor growth, but did inhibit metastasis formation; at cellular level, genistein inhibited the vascular endothelial growth factor receptor (FLT4) and metalloproteinase 2; FLT4 is a marker of metastatic disease and response to small molecule therapies that inhibit CRC metastasis.

Regarding studies in humans, a clinical trial with 13 patients with metastatic CRC histologically confirmed and who had not received treatment evaluated the safety and tolerability of genistein (60 mg/day), four days before and during treatment (1-3 days) with chemotherapy (folfox or folfox – bevacizumab (combination of 5FU and oxaliplatin with or without anti-angiogenic agent bevacizumab); the most-common adverse events related with genistein included headache, nausea, and hot flushes. No increase was observed of adverse events related with chemotherapy when genistein was added. Best overall response (BOR) rate and the median progression-free survival (PFS) were 61.5% and 11.5 months, respectively. In this study it was noted that adding genistein to folfox or folfox-bevacizumab was safe and tolerable. (Pintova *et al*., 2019). The results described herein confirm the role of this isoflavone in prevention and as adjuvant in the treatment of neoplasms in the colon.

Kaempferol

A study evaluating the effect of kaempferol on the tissue lipid peroxidation and antioxidant status in male Wistar rats with DMH-induced CRC compared the effectiveness of this flavonoid with that of irinotecan (200 mg/kg), a specific inhibitor of DNA topoisomerase I, found that in groups receiving a daily oral dose of 50, 100, or 200 mg/kg of body weight of kaempferol for 16 weeks, DMH-induced erythrocyte lysate was reduced and the level of hepatic thiobarbituric acid reactive substances increased enzyme antioxidant catalase, superoxide dismutase and glutathione peroxidase. Recovery of the enzymatic state was maximum at the dosage of 200 mg/kg of body weight and was comparable with irinotecan, showing that kaempferol could be used safely as chemo-preventive agent in CRC (Nirmala & Ramanathanb, 2011).

Another study evaluated the effect of kaempferol to alleviate inflammatory responses of DSS-induced ulcerative colitis (UC) in mice. The C57BL/6J female mice were divided into groups: a negative control group, a control group with DSS, and groups of DSS + kaempferol at 0.1% or at 0.3% before or after feeding. The results showed significant decrease in plasma nitric oxide (NO) levels and PGE2 in groups treated with kaempferol at 0.3% before and after feeding. The plasma level of Leukotriene B4 (LTB4), involved in inflammation, was profoundly reduced in all animals fed with kaempferol. The myeloperoxidase (MPO) activity of the colonic mucosa was also suppressed in groups treated with 0.3% kaempferol before or after feeding. The RNAm of TFF3, a marker of the goblet-cell function, was upregulated in animals pre-fed with kaempferol, indicating that kaempferol is an effective anti-inflammatory agent that protects the colonic mucosa from the DSS-induced UC. Dietary kaempferol administered prior to the induction of the colitis was more effective in suppressing some of the markers associated with colitis (Park *et al*., 2012).

Gallic acid

With respect to this polyphenol, a study investigated the effectiveness of supplementing with Gallic acid (GA) on tissue lipid peroxidation and the antioxidant defense system in DMH-induced colon carcinogenesis in male Wistar rats. The rats were classified into groups, which included controls (normal diet, group treated with DMH + normal diet),

one group that received GA (50 mg/kg of body weight) orally together with the normal diet, and three additional groups that received GA together with DMH during the onset, post-onset stages and throughout the study period, respectively; the results showed in the groups with GA supplement a decrease of lipid peroxidation products, decreased levels of enzymes superoxide dismutase, catalase, reduced glutathione, glutathione reductase, and glutathione peroxidase (Giftson *et al*., 2010).

Another study evaluated, in rats with DMH-induced CRC, the potential role of GA (50 mg/kg of body weight/30 weeks) in drug metabolizing enzymes. This research measured the activities of phase I enzymes (cytochrome P450 and cytochrome b5) and phase II enzymes (glutathione S-transferase, DT-diaphorase and gamma glutamyl transpeptidase) in liver and colon. The results show, in the controls, a decrease in the activities of phase II enzymes and an increase in the activities of phase I enzymes. With GA supplementation, the reverse was proven, that is, significant increase in the activities of phase II enzymes and significant decrease in the activities of phase I enzymes, in addition to the decrease in tumor incidence, with histopathological changes (Giftson *et al*., 2011).

Data from these studies suggest that GA could exert a significant chemo-preventive effect on colon carcinogenesis in animal models.

EGCG

Studies in animals indicate that EGCG can reduce colon tumorigenesis; for example, in rats with AOM-induced CRC, the EGCG reduced the number of tumors these animals developed, with this effect associated with the reduction of the Wnt signaling pathway and COX2 expression (Ogawa *et al*., 2012), and argue that EGCG contributed directly to tumor suppression by producing changes in the severity of the inflammation.

In ApcMin/+ mice (model of multiple intestinal neoplasms), treatment with EGCG present in green tea restored the levels of RXRα protein (transcription factor and intracellular receptor for thyroid hormones and steroids), and expression of this gene due to reduced methylation of the RXRα promoter (Morris *et al*., 2016). Another CRC animal model, in this case induced by a xenograft of spheroid-derived cancer stem cells, demonstrated that treatment with EGCG produced inhibition of tumor growth; furthermore, and according to the authors, these data provide new and unrecognized evidence for EGCG-induced sensitization to 5FU through the selection of cancer stem cells in CRC (Toden *et al*., 2016).

Regarding studies in humans, evidence shows that consumption of EGCG present in green tea provoked changes in intestinal microbiome, which included increase of bacteria (Lachnospiraceae, Bifidobacteriaceae, and Ruminococcaceae) producers of short-chain fatty acids, decrease in potentially pro-inflammatory bacteria, such as the genus Prevotella that are increased in patients with CRC (Elinav *et al*., 2011; Yuan *et al*., 2018); however, they could not show direct association of these changes and EGCG intake.

Caffeic acid (CA)

The evaluation of the action of caffeic acid and its CAPE and CAPPE derivates in a mouse xenograft model showed that consumption of these two polyphenols inhibited significantly colorectal tumor growth; the mechanisms included modulation of the PI3-k/Akt, AMPK, and m-TOR signaling cascades (Chiang *et al*., 2014).

Another study revealed that decyl caffeic acid (DC) differentially suppressed cell growth, and the therapeutic advantage appeared to depend on autophagy. In addition, consumption of DC blocked colorectal adenocarcinoma tumor growth in an experimental animal model (Chen *et al*., 2020). These results suggest that DC could act as a therapeutic agent through the significant suppression of tumor growth of human CRC cells.

In general, preclinical studies, using *in-vivo* models, have implied the polyphenols present in the diet on a broad range of activities against cancer, among them: antiproliferative activities, cell cycle blockage, DNA alteration and repair, induction of apoptosis, anti-inflammatory activation of tumor suppressing genes, oncogene suppression, regulation of hormone levels and growth factors, and inhibition of invasion, angiogenesis, and metastasis. The mechanisms of these phytochemicals and their effects against colon cancer are illustrated in Table No. 2.

Table No. 2
Evidence of preclinical studies on the use of phytochemicals for CRC prevention and treatment and their associated molecular effects

Phytochemical	Dose	Colorectal Cancer Model	Results	Reference
Quercetin	50 mg / kg/IP 1 time a week/5weeks	Mice/DMH	Decreased Oxidative stress markers, and carcinoembryonic antigen plasma levels	Saleem *et al*., 2015
	10mg/kg/iv/3 days/5 times)	Mice/xenograft CT26 cells	Decreased expression Hsp70. Increased apoptosis induced by hyperthermia and thermo chemotherapy	He *et al*., 2013
Ruthenium-quercetin complex	50-200 mg/kg/oral gavage/18 weeks	Male Wistar rats DMH/DSS	Decreased multiplicity of ACF, hyperplastic lesions, cell proliferation, CAT, SOD and glutathione levels. Increased apoptosis, p53 and Bax gene, decreased expression of BCl2	Roy *et al*., 2018
anthocyanin-rich bilberry extract.	1-10 %; 9 weeks.	Female Balb/c mice/ AOM-DSS	Prevented the formation and growth of colorectal cancer	Lippert *et al*., 2017
Genistein	5-45 mg/kg,	Wistar rats / DMH	Suppresses cancer progression ↓ PCNA, ↑ Nrf2, HO-1, ↓ β-Catenin	Sekar *et al*., 2016
Genistein	140 mg/kg; 3 week gestation and 4-week lactation periods	Male Sprague-Dawley rats	Decrease aberrant crypts and aberrant crypt foci.	Zhang *et al*, 2013
EGCG/in green tea)	0.1% EGCG/drinking water; 4 weeks,	male F344 rats/AOM	decreased ACF; Suppress the occurrence of colonic preneoplastic lesions	Ogawa *et al*., 2012
Kaempferol	50, 100, 200 mg/kg BW/ 4 weeks	male Wistar Rats/ DMH	Lowered erythrocyte lysate and liver thiobarbituric acid reactive substances level and rejuvenated antioxidant enzymes: catalase, super oxide dismutase and glutathione peroxidase.	Nirmala & Ramanathan, 2011
Gallic acid	50 mg/kg bw/30 weeks	Wistar Rats/DMH	increase GST, DT-diaphorase and γGTP. Decrease cytochrome P450 and cytochrome b5 activities and tumor incidence	Giftson *et al*., 2010
Resveratrol	Resveratrol along Resveratrol + DMH; 30 weeks	White outbred male rats	Inhibition lipid peroxidation.	Rytsyk *et al*., 2020

Curcumin	*Il10−/−* mice10/AOM	increased survival, bacterial richness; decreased colon weight/length ratio, and at 0.5%, entirely eliminated tumor burden.		McFadden 2015
	20 weeks			

IP: intraperitoneal injection; DMH: 1, 2-dimethylhydrazine; AOM: azoxymethane; DSS: dextran sulfate sodium; CRC: colorectal cancer; ACF: aberrant crypt foci. CAT: catalase; SOD: superoxide dismutase; bw: body weight. GST: glutathione S-transferase; DT-diaforase: NAD(P)H:quinone oxidoreductase; γGTP: gamma glutamil transpeptidase. For other acronyms in the table see list of abbreviations

Clinical studies, have implied the polyphenols present in the diet on some activities against cancer, among them: 40% reduction in ACF number, tumor tissue proliferation decreased, Best overall response rate, and median progression-free survival. However, many of these studies are inconclusive or no direct relationship was found. These phytochemicals and their effects against colon cancer in human are illustrated in Table No. 3.

Table No. 3
Evidence of clinical studies on the use of phytochemicals for CRC prevention and their associated molecular effects

Phytochemical	Concomitant therapy	Dose, duration, groups	Study Type	Effects	Reference
Quercetin	NSAID	1163 cases, 1501 controls 45-80 years old	Cases - control	Decreases risk of CRC when fruit intake is high.	Djuric *et al.*, 2012
Flavonoids and derivatives, anthocyanins	Aspirin y NSAID	118.842 (42.478 men, 76.364 women) follow-up: 26 years	Prospective cohort	No association with CRC	Nimptsch *et al.*, 2016
Dietary flavonoids	Not described	477,312 adult participants (10 European countries); Follow-up 11 years	Prospective cohort	No association between the total intake or flavonoids in CRC	Zamora-Ros *et al.*, 2017
Anthocyanins	Not Concomitant therapy	13 patients with ulcerative colitis; 9 weeks	Pilot	A decrease in endoscopic Mayo score and histologic Riley index.	Biedermann *et al.*, 2013
	Not Concomitant therapy	25 patients 0.5-2.0 grams anthocyanins) daily/7 days	Pilot	Tumor tissue proliferation was decreased by 7%	Thomasset *et. al.*, 2009
Genistein	FOLFOX or FOLFOX-Bevacizumab	13 patients Oral, 60 mg/day/7 days/2 weeks, beginning 4 days prior to chemotherapy and continuing through days 1-3 of	Cases	Best overall response rate (BOR), and median progression-free survival (PFS).	Pintova *et al.*, 2019

		infusional chemotherapy			
Curcumin	Not Concomitant therapy	20 patients 2 g/day 20 patients 4 g/day 30 days	Patients	40% reduction in ACF number with the 4 g dose	Carroll *et al*., 2011

NSAID= nonsteroidal anti-inflammatory drugs; CRC: colorectal cancer; ACF: aberrant crypt foci

DISCUSSION

The literature reviewed evidences the positive effect of polyphenols on CRC prevention, tumor regression, metastasis, and treatment. Studies in CRC cell models revealed that the anticancer effects of these polyphenols are exerted on the signaling pathways implied in proliferation and in cell death; their antiproliferative action seems to concentrate on diminishing the activities or expression of antiapoptotic proteins, like p-Akt, Wnt/β-catenin, Bcl-2, Bcl-xl, NF-kB, RXR-α, Survivin, Erk1/2 and metalloproteinases among other biomarkers, (Zhang *et al.,* 2016a, Chen *et al.,* 2016, Yuan *et al.,* 2016).

The pro-apoptotic effects of polyphenols focus on the increase and activation of caspases 3, 7, 8, and 9, detention of the cellular cycle in different phases, specially Go/G1, and on lysosomal and mitochondrial damage; the last implies release of cytochrome c, which activates cell death through the cascade of caspases.

The increase of oxidative stress to promote cell death and activation of factors, such as p53, the pathway of the MAPK family of kinases, and the ROS among other factors are other proapoptotic effects of polyphenols.

At the level of studies in animal models, the review shows that polyphenols diminish the number of foci and aberrant crypts, of hyperplastic lesions, prevent tumor formation and growth, improves the survival of animals treated with these phytochemicals, and upregulates a series of biomarkers, like catalase antioxidant enzymes, superoxide dismutase, and glutathione oxidase.

Regarding studies in humans, the results are les conclusive, Although the intake of flavonoids and non-flavonoid polyphenols decreases the risk of CRC, the proliferation of cancer cells extracted from biopsies, the number of crypts and foci of aberrant crypts and promotes changes in the intestinal microbiome associated with CRC risk, it has not been possible to demonstrate in humans a direct effect of each of the polyphenols in the regression or reduction of tumors in CRC.

Recent studies have indicated that these compounds could have significant synergistic effects with each other and with other anticancer agents on preventing carcinogenesis, tumor progression, and apoptosis. Additionally, it has been demonstrated that the application of specific phytochemicals attenuates resistance to agents currently used in CRC chemotherapy. However, despite inconclusive *in-vivo* studies in humans, it is considered that constant and adequate intake of polyphenols present in the diet can prevent CRC, are safe and can be used as adjuvants in treatment, so the need remains to delve further into research in humans, especially on the digestibility, bioavailability, synergy and absorption of polyphenols and on the possible metabolites derived from the digestion of these compounds; it is also important to delve into dosage and frequencies of the intake.

CONCLUSION

Flavonoid-type phytochemicals and polyphenolic acids are safe for human health, acting as therapeutic supplements to reduce CRC risk, helping in the treatment and arrest of its progression and to revert some pathological states and as sensitizers to anticancer treatment.

These effects take place due to their inhibitory action of anti-apoptotic pathways and activation of pro-apoptotic pathways. It was also shown that they are capable of reducing inflammatory states and the intestinal microbiome associated with CRC generation.

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