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Review article

Natural polyphenols: A protective approach to reduce colorectal cancer

Joel Okpoghono [a,*], Endurance F. Isoje [b], Ufuoma A. Igbuku [c], Ovigueroye Ekayoda [d], Godson O. Omoike [e], Treasure O. Adonor [f], Udoka B. Igue [g], Solomon U. Okom [a], Faith O. Ovowa [b], Queen O. Stephen-Onojedje [d], Ejiro O. Ejueyitsi [d], Anita A. Seigha [g]

[a] Department of Biochemistry, Faculty of Science, Delta State University of Science and Technology, Ozoro, Delta State, Nigeria
[b] Department of Science Laboratory Technology (Biochemistry Option), Delta State University of Science and Technology, Ozoro, Delta State, Nigeria
[c] Department of Chemistry, Faculty of Science, Delta State University of Science and Technology, Ozoro, Delta State, Nigeria
[d] Department of Biochemistry, Faculty of Science, Delta State University, Abraka, Delta State, Nigeria
[e] Department of Public Health, School of Health and Society, University of Wolverhampton, United Kingdom
[f] Department of Biotechnology, Faculty of Life Science, University of Essex, United Kingdom
[g] Department of Chemical Sciences, Novena University, Ogume, Delta State, Nigeria

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ABSTRACT

Background: A form of cancer that affects the rectum or colon (large intestine) is called colorectal cancer (CRC). The main risk factors for CRC include dietary, lifestyle, and environmental variables. Currently natural polyphenols have demonstrated impressive anticarcinogenic capabilities. *Objective:* The main objective was to provide an updated, thorough assessment of the defensive mechanism of natural polyphenols for the global suppression of colorectal cancer. More precisely, this study aimed to analyze a set of chosen polyphenols with demonstrated safety, effectiveness, and biochemical defense mechanism on colon cancer models in order to facilitate future research. *Methods:* This review was carried out with purposefully attentive and often updated scientific databases, including PubMed, Scopus, Science Direct, and Web of Science. After selecting approximately 178 potentially relevant papers based just on abstracts, 145 studies were meticulously reviewed and discussed.

Abbreviations: AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; APC, Adenomatous polyposis coli; Bax, BCL2 associated X; BCL2, B-cell lymphoma 2; BRAF, B-type Raf proto-oncogene; Caco-2, Cancer coli-2; CaM, calmodulin; cdc25A, Cell division cycle 25A; CDC4, Cell division control protein 4; CDK, Cyclin-dependent protein kinases; CIMP, CpG island methylator phenotype; CIN, Chromosomal instability; Cox-2, Cyclooxygenase-2; CRC, Colorectal cancer; CSCs, Cancer stem cells; DDS, drug delivery systems; EGCG, epigallocatechin gallate; EGF, Epidermal growth factor; FOXO3, Forkhead box O3; GALNT11, Polypeptide N-Acetyl-galactosaminyl transferase 11; HL60, human promyelocytic leukemia cell line; IFN-γ, Interferon-gamma; IGF-2R, Insulin-like growth factor-2 recptor; JAK/STAT, Janus kinase/signal transduction and transcription activation; KRAS, Kirsten rat sarcoma virus; LOH18q, Loss of heterozygosity for the long arm of chromosome 18; MAPK, mitogen-activated protein kinase; miRNAs, Micro Ribonucleic acids; MMP, Matrix metalloproteinase; MMP9, matrix metalloproteinase-9; MSI, microsatellite instability; NF-κB, Nuclear factor kappa B; Nkd2, Naked cuticle 2; NLPs, Nanostructured lipid particles; OXA, oxaliplatin; p53, Tumor protein 53; PPL, piperlongumine; pRb, retinoblastoma protein; pRB, Retinoblastoma protein; ROS, Reactive oxygen species; SCFAs, Short-chain fatty acids; SMAD4, Decapentaplegic family member 4; SNAC, Sodium N-[8-(2-hydroxybenzoyl) amino] caprylate; TGF-βR, Transforming growth factor-beta receptor; TNFα, Tumour necrosis factor alpha; TP53, Tumor protein p53; TRPV1, Transient receptor potential vanilloid 1; TS, Thymidylate synthase; uPA, plasminogen activator.

* Corresponding author.
E-mail addresses: okpoghono@gmail.com, okpoghonoj@dsust.edu.ng (J. Okpoghono).

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Results: The outcomes disclosed that anti-CRC mechanisms of natural polyphenols involved the control of several molecular and signaling pathways. Natural polyphenols have also been shown to have the ability to limit the growth and genesis of tumors via altering the gut microbiota and cancer stem cells. However, the biochemical uses of many natural polyphenols have remained restricted because of their truncated water solubility and low bioavailability. In order to attain synergistic properties it is recommended to combine the use of different natural polyphenols because of their low bioavailability and volatility. However, the use of lipid-based nano- and micro-carriers also may be helpful to solve these problems with efficient distribution system to target sites.

Conclusion: In conclusion, the use of polyphenols for CRC treatment appears promising. To ascertain their efficacy, more clinical research is anticipated.

1. Introduction

The second most common cause of mortality for cancer patients is colorectal cancer (CRC), a common gastrointestinal cancer [1]. The third most prevalent type of cancer worldwide is CRC, and its incidence is still on the rise [2]. Numerous variables contribute to the pathophysiology of CRC, including genetics, food habits, lifestyle choices (such as consuming large amounts of processed meat, drinking alcohol, and smoking), and being overweight [2–5]. Although CRC treatment has advanced recently, the 5-year survival rate for patients remains poor. This underscores the necessity for novel therapeutic methods against CRC and shows the shortcomings of traditional treatments, such as surgery, chemotherapy, radiation, and immunotherapy.

Natural plant-based yields have garnered significant interest recently because of their prospective applications as preventative and chemotherapeutic medicines for cancer [6]. Plants naturally contain antioxidants called polyphenols, and the kinds and concentrations of these substances differ greatly amongst fruits, vegetables, leaves and spices [7–11]. There are several known naturally occurring polyphenols, such as flavonoids, phenolic acids, polyphenolic amides, and other polyphenols [6,7,12]. Phenolic acids and flavonoids constitute around 30 % and 60 % individually, of the polyphenols that are now known to exist. Similarly, it has been shown that other significant polyphenols, such resveratrol and curcumin, are active in treating a variety of illnesses. Polyphenols have a variety of physiological functions, including antibacterial, antioxidant, anti-inflammatory, antimalarial, antiviral, antitumor, and immunomodulatory properties [13],14. They may be able to also lessen the oxidative damage of enzymes and DNA in cells and tissues.

Polyphenols are thought to be a significant source of natural medications for management of many diseases because of their exceptional efficacy and safety [15–17], as evidenced by the various studies that have demonstrated their impact of inhibition on CRC [6,13,14]. Nevertheless, there are a number of restrictions on the therapeutic uses of phenolic chemicals. According to Ahmad et al. [18], these compounds exhibit the feature of being poorly soluble in water and are readily destroyed by environmental variables like light, temperature and pH. As a result, they have low bioavailability and poor absorption [16,19]. Furthermore, phenolic compounds biological impacts are compromised and its curative effect is diminished by high metabolism and quick clearance [18,20]. Drug delivery systems (DDSs) with a diversity of features that are biocompatible are established as a solution to these issues [18,21]. DDSs are intended for the controlled release of pharmaceuticals at the right doses in a targeted manner. Polyphenols DDSs frequently aim to increase the bioaccessibility and bioavailability of the compounds by improving their steadiness and solubility [14]. Additionally, by avoiding medication overdose and its associated negative effects, high loads and targeted distribution optimize polyphenols bioactivity [22]. Recently, many research have attempted to optimize the anticancer benefits of polyphenols [6,14]. To give researchers more insight into studying the intake of natural polyphenols and developing novel medications derived from natural polyphenols for CRC treatment, the present review discussed the progress of studies on natural polyphenols for the management of CRC, also highlights current research that uses the DDSs to enhance polyphenols' anticancer properties.

2. Methodology

The search for data on natural polyphenols defensive mechanism for suppression of colorectal cancer was conducted by taking into account all scientific articles published through Science Direct, Medline (Pubmed), and other electronic research engines up until January 2024. As additional resources, a few published books were consulted. The English language comprised the bulk of the material that was examined. The search employed "MeSH terms" in addition to sporadically "free text" terms. Following an initial screening of obtained articles (about 178), chosen publications (145 total) were read and scrutinized based on their titles and abstracts. Most of these studies concentrate on several molecular and signaling pathways and anti-CRC mechanisms of natural polyphenols for suppression of Colorectal Cancer.

3. Molecular basis of colorectal cancer and chromosomal instability (CIN) pathway

Controlling of CRC carcinogenesis involves both genetic and epigenetic changes [3,4]. The transition from normal colorectal epithelium to an adenoma and then, ultimately, to an invasive and metastatic tumor was clarified in 1980, which is when the adenocarcinoma sequence was first characterized [23]. The chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) pathways are the three main routes underlying the genomic instability of CRC and its etiology

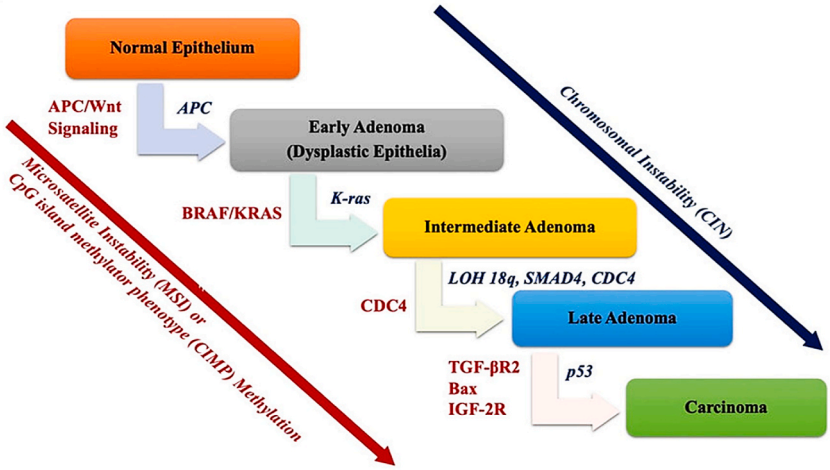

Fig. 1. Multistep genetic model for colorectal adenocarcinoma sequence. The chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) hypermethylation are the three pathways that control the adenocarcinoma sequence [23].

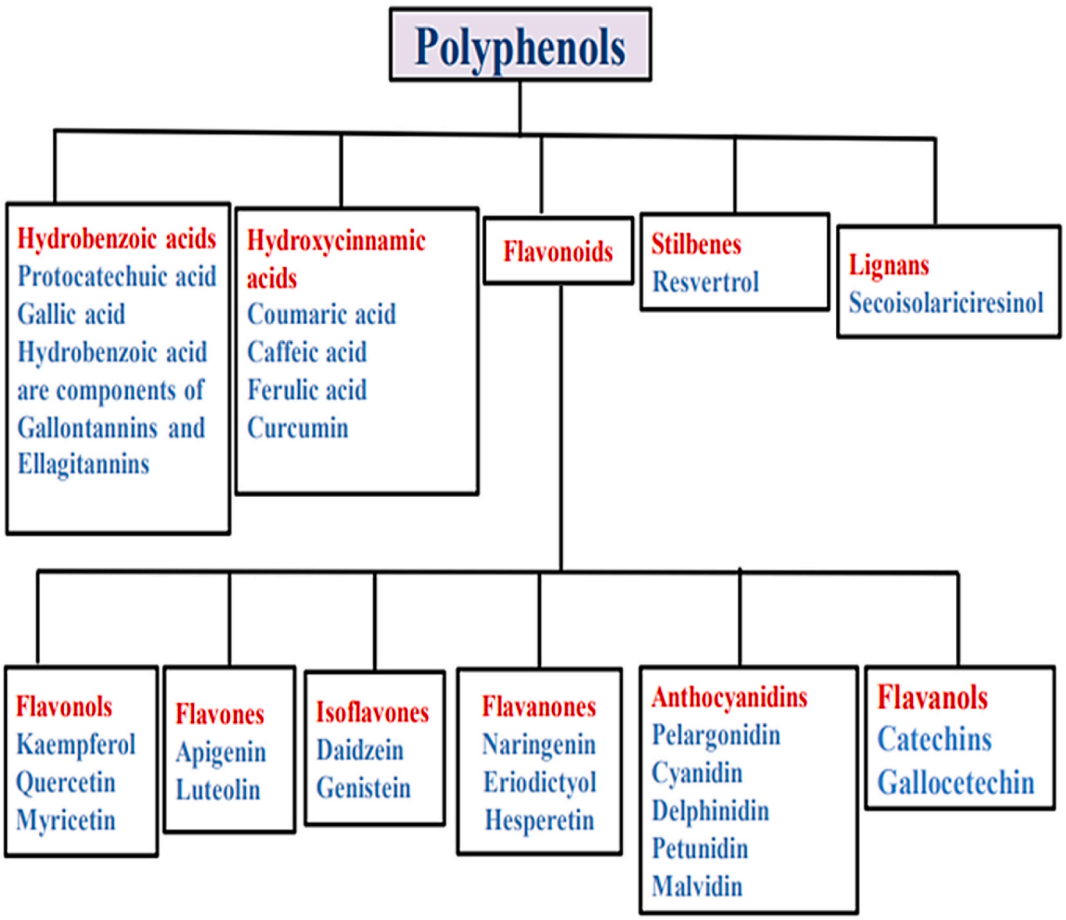

Fig. 2. Polyphenol classifications.

(Fig. 1). The most frequent genetic instability in CRC is called chromosomal instability, which is defined as a marked increase in the gain or loss of big or complete chromosomes. About 85 % of adenocarcinoma changes have CIN, which is defined by loss of heterozygosity of chromosome 18 long arm (18q LOH), TSGs inactivation (APC and TP53), and oncogenes activation (KRAS and BRAF), all of

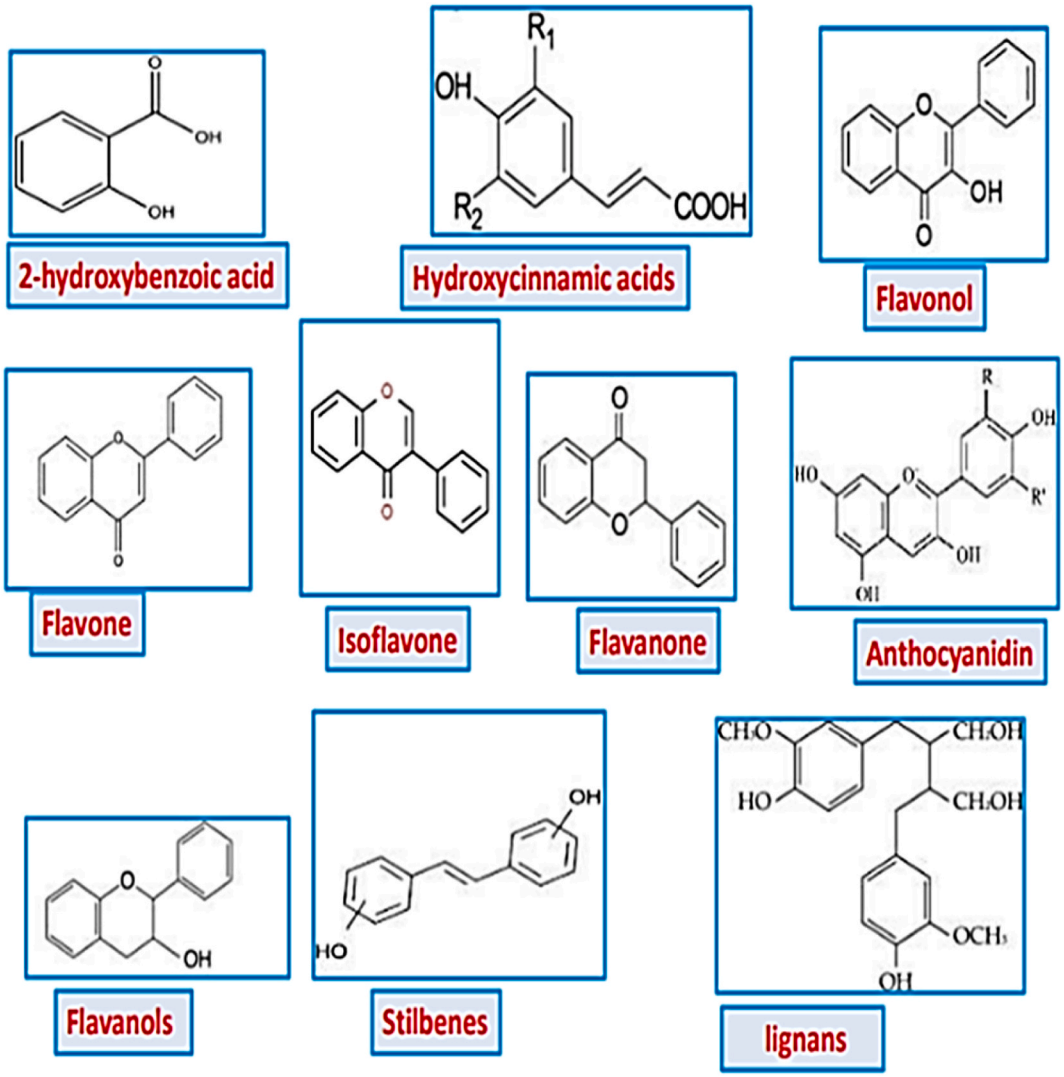

Fig. 3. Structure of polyphenols.

Table 1
The main sources of natural polyphenols in the diet.

Items	Natural sources
Hydrobenzoic acids	Gallotannins in mangoes and ellagitannins in red fruits such as strawberries and raspberries
Hydroxycinnamic acid	Plums, apples, red berry fruits, walnuts, apricots, blueberries, and tomatoes.
Flavonols	Fruits, vegetables, and beverages, beer, tea, cocoa, pulses, spices
Flavones	Onion, apple, cherry, broccoli, tomato
Isoflavones	Soy, leguminous plants
Flavanones	Tomatoes, pulses, aromatic plants, aromatic plant
Anthocyanidins	Flower petals, fruits, vegetables, varieties of grains, black rice
Flavanols	Tea, red wine, chocolate, skins of grape, skins of apple, blueberry
Stilbenes	Resveratrol and piceatannol, a resveratrol metabolite are found in grapes (skin), peanuts, and red wine
Lignans	Cereals, soybeans, broccoli, cabbage, apricots and strawberries.

Source: Khan et al. [37].

which stimulate CRC carcinogenesis [24–26].

The adenocarcinoma sequence model has been linked to genetic anomalies in TGF-βR and PI3KCA in the past [27–29]. According to Diep et al. [30] and Jasmine et al. [27], the existence of potential TSGs or oncogenes indicates the allelic loss or gain of material. This allows altered cells to proliferate and eventually turns normal cells into malignant ones. The CIN, MSI, and CIMP hypermethylation are

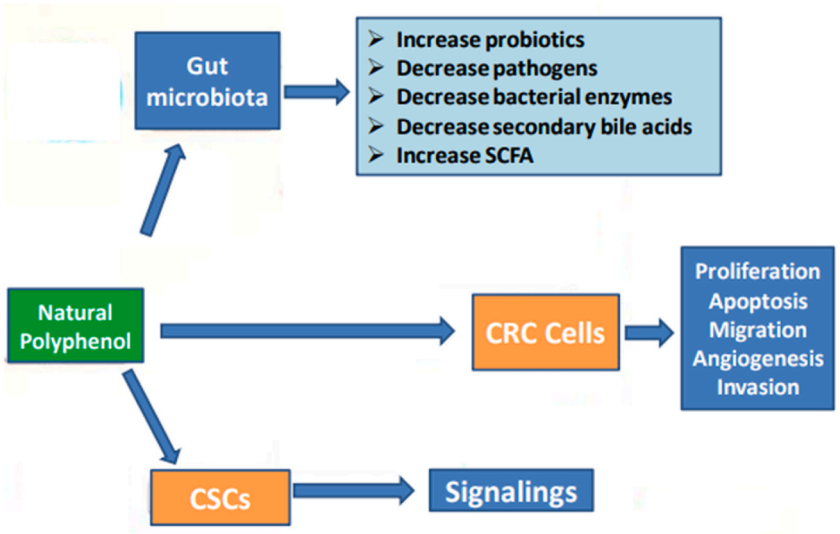

Fig. 4. The role of polyphenols in the gut microbiota, CSCs and CRC. Natural polyphenols exhibit anti-cancer activities via controlling CSCs and gut microbiota which may activate and increase probiotics and SCFA, and decreases pathogens, bacterial enzyme and secondary bile acids. The benefits of natural polyphenols are also linked to the control of several molecules and signaling pathways, as well as the encouragement of apoptosis and the suppression of CRC cells invasion, migration, and proliferation.

the three mechanisms that control the adenocarcinoma sequencing.

4. Classes of natural polyphenol

The fruits, roots, flowers, and leaves of plants contain over 8000 naturally occurring polyphenol products. These products are classified as secondary metabolites and are mainly benzene rings that can bind to several hydroxyl groups or occasionally to aromatic carbon [31,32]. According to reports, polyphenols are generated through the shikimate or acetate pathway and have a range of advantageous properties, such as antioxidant properties [33–36], preservation of intestinal microecological balance, and cell death suppression [37,38]. Research indicates that the intestine absorbs just 5–10 % of polyphenols, whereas other tissues such as the liver, adipose, and skeletal muscle receive 90–95 % of polyphenols (Fig. 2). Natural polyphenol products are categorized as flavonoids (flavones, flavonols, isoflavones, neoflavonoids, chalcones, and anthocyanidins) or non-flavonoids (phenolic acids, stilbenoids, and phenolic amides) on the basis of the various substituents on benzene rings (Fig. 3, Table 1) [39,40].

The conversion of high molecular weight polyphenols to bioactive metabolites is one process in which gut microorganisms are crucial to dietary polyphenols digestion and absorption [41]. After being carried to the colon, the colonic microbiota can hydrolyze and metabolize the polyphenols to create aromatic acids [41,42]. The metabolites of polyphenols enter the liver when they are broken down in the colon or small intestine. The majority of these metabolites originate in liver, travels via portal vein to every area of the body, where they take part in different metabolic processes such as sulfation, glucuronidation, and methylation [41]. Furthermore, some unabsorbed metabolites are expelled in the feces, and some other metabolites are eliminated as bile components that are renewed by intestinal microbial enzymes prior to reabsorption [42].

4.1. Polyphenols and the gastrointestinal tract microbiota

The significance of a homeostatic gut microbiota for the host's general health is widely acknowledged. Diverse species of intestinal bacteria coexist in a dynamic balance that is sensitive and readily disrupted by intestinal carcinogenesis, which can result in dysbacteriosis [43]. According to Tjalsma et al. [44], a potential model of the connection between microbiota and CRC suggested that specific commensal gut bacteria may damage DNA and cause gene mutations in epithelial cells of intestine. These changes in intestinal microenvironment could then lead to growth of specific opportunistic pathogens.

The emergence of pathogenic microbiota is another factor in the progression of cancer. For instance, *Fusobacterium nucleatum* causes CRC cell proliferation, reactive oxygen species (ROS) production, and DNA damage to initiate oncogenic processes. Extracellular free radicals produced by *Enterococcus faecalis* exacerbate the chromosomal instability linked to colorectal cancer. Additionally, certain other gut microorganisms, including *Bacteroides fragilis, Clostridium septicum, Escherichia coli,* and *Streptococcus bovis*, are connected to the emergence and progression of CRC. Thus, maintaining a homeostatic intestinal milieu and controlling gut microbiota might be a potential strategy for treating CRC [45].

Zhang et al. [43] discuss the application of natural polyphenols in CRC treatment. The therapeutic and prophylactic efficacy of natural polyphenols against CRC are attributed to mechanisms involving the regulation of several molecules and signaling pathways, the proliferation of cancer cell suppression, migration, invasion, and apoptosis promotion (Fig. 4). The author further stated that,

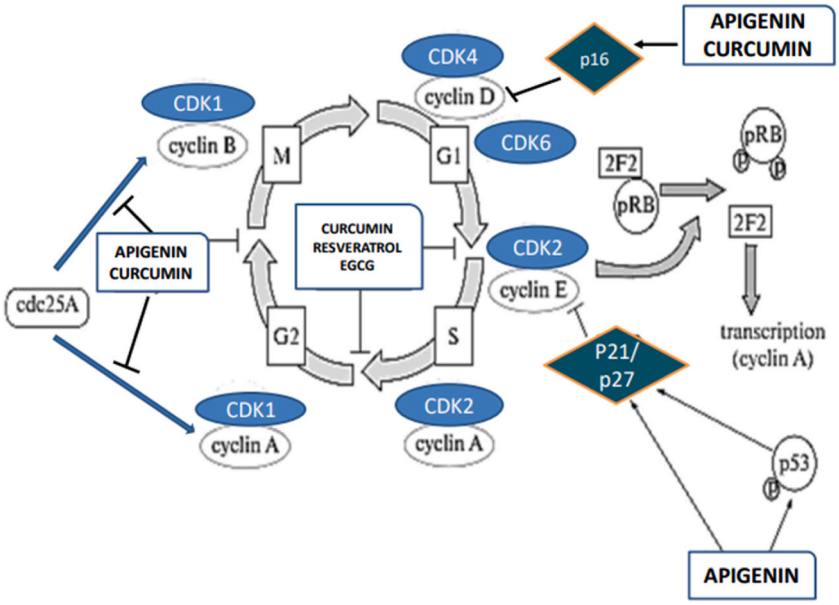

Fig. 5. Regulation of cell cycle. Apigenin and curcumin suppresses cyclin A, B and the cell cycle phase G2 to M. Curcumin resveratrol and EGCG suppresses G1 and S phase of the cell cycle. Also, apigenin and curcumin astimulates p16 to inhibit cyclin D. Apigenin stimulates the phosphorylation of p53 which further stimulates p21/p27 to suppress cyclin E. Symbol show inhibitory (⊥) effects of polyphenols.

natural polyphenols have anti-cancer effects through controlling gut microbiota and cancer stem cells (CSCs), and are believed to be important in the genesis of CRC. Consequently, the possible processes underpinning the usage of different common polyphenols has been presented, together with research on polyphenols monitoring action on CSCs and gut microbiota in CRC patients.

Also, polyphenols control the gut microbiota by encouraging probiotic colonization and inhibiting opportunistic infections, which helps to restore the balance of microorganisms in the gut [46–48]. The anticancer benefits of gut microbiota-produced polyphenol metabolites against CRC may enhance the overall effectiveness of polyphenols. Zhang et al. [49] conducted a study that examined quercetin cytotoxicity and its metabolites on various cell lines related to colon cancer. In comparison to quercetin, the metabolites formed by particular gut microbiota, such as *Bacteroides fragilis* and *Clostridium perfringens*, substantially inhibited certain cell lines.

4.2. Polyphenols modulate cancer stem cells (CSCs)

The invasion of CSCs is a primary cause of tumor therapy failure [43]. According to Du et al. [45], CSCs possess self-renewal capability and differentiation, as well as possessing regenerative capabilities for metastasis and carcinogenesis. Typically, CSCs are found at an inactive cell cycle stage and not affected by chemotherapy or radiation therapy. Tumorigenicity and the presence of metastatic potential are the hallmarks of colonic CSC markers (CD133, CD44, CD29, CD24, EpCAM, ESA, and LGR5) [45]. These markers work well as discriminators of CSC viability. Consequently, CSCs provide a significant obstacle to drug resistance management, metastasis, tumorigenesis and tumor relapse. Polyphenols could be useful in treating CRC via targeting signaling pathways or CSC surface markers.

GO-Y030, a novel curcumin analog, reduced colonic CSCs' survival, prevented tumorsphere development, and accelerated apoptosis by down regulating the STAT3 pathway [43]. In chemo-resistant colorectal cancer cells, curcumin difluorinated (CDF), an analog of curcumin, decreased CSC marker levels, repressed proliferation, and broke up the colonospheres. CSCs were more prevalent in these chemoresistant cells. According to Roy et al. [50] the miRNA-21-PTEN-Akt axis mediated the suppression of CDF on CSCs. Akt expression was decreased as a result of CDF's up regulation of the PTEN pathway and down regulation of miRNA-21. According to Toden et al. [51] epigallocatechin-3-gallate elevated self-renewal inhibitory miRNAs and downregulated the Notch1 pathway, which prevented CSCs from proliferating and reduced their ability to withstand chemoresistance. Another study found that resveratrol treatment reduced CSC susceptibility to chemotherapeutic drugs and their ability to proliferate; this was also correlated with enhanced autophagy signaling and GALNT11 (Polypeptide N-Acetylgalactosaminyltransferase 11) inhibition [52]. Generally speaking, GALNT11 expression is linked to cancer and tumor recurrence. The aforementioned results suggest that polyphenols have promising therapeutic potential against CRC by modulating several pathways in CSCs [52].

4.3. Polyphenols stop the growth of tumor cells by stopping the cell cycle

Eukaryotic cells divide strictly according to a cell cycle that has four distinct phases: mitosis (M) (division of chromosomes followed by cell division), S (DNA synthesis), G2 (an intermediary phase preceding nuclear division), and G1 (cell formulation for DNA

replication) [52]. At specific points in cell cycle, there are multiple checkpoints that coordinate subsequent phase-specific events. The G1 checkpoint, the G1/S phase transition checkpoint, the G2/M phase transition checkpoint, and the metaphase-anaphase transition checkpoint are the four main checkpoints. Cyclin-dependent protein kinases (CDK) are responsible for controlling cell cycle transition. They become active when they bind to cyclin proteins (Fig. 5). By interacting with different cyclins, CDK family members contribute to signal transduction that drives the genes expression which code for products needed for the next phase of cell cycle [53]. For illustration, let's look at the G1 to S phase transition. Growth features and other stimuli initially causes production of cyclin E, which in turn activates CDK2 [52]. The complex containing the transcription factor (E2F) and the retinoblastoma protein (pRb) is phosphorylated by this kinase. This factor detaches from the phosphorylated pRb and initiates genes transcription essential for DNA synthesis, such as thymidine kinase and dihydrofolate reductase.

Additionally, the cyclin A—CDK2 complex that initiates the S G2 transition is repressed by p21 protein. Moreover, cytoplasmic Kip1 family proteins, in particular p27, function as inhibitors (Fig. 5). Therefore, arrest of cell cycle at a specific phase is provided via negative control of cell cycle. The primary cause of cell cycle regulator failure in neoplastic cells is disparity in regulatory molecules. The constitutive functioning of transcription factors linked to positive regulation of proliferation and elevated cyclin levels characterize these cells [54].

Numerous plant polyphenols stops tumor cell growth by arresting cell cycle (Fig. 5), and the ways they do so vary based on the kind of tumor cell line [55,56]. For instance, resveratrol initiated the arrest of cell cycle at the G1 phase in epidermoid carcinoma A431 cells, while it stopped the cell cycle at the S/G2 phase transition in leukemic promyelocytes HL60, lymphoma U937 cells, colorectal cancer CaCo2 cells, and cells from mammary gland, intestine, and prostate [57]. According to Eom et al. [57], resveratrol increased the synthesis of the inhibitory protein p21 while decreasing the levels of cyclins D1, D2, and E, along with cyclin-dependent kinases CDK2 and CDK4/6. Only the colorectal tumor SW480 cell line revealed reduced manifestation of cyclins D1 and A due to resveratrol; cyclin D1 levels were lowered by resveratrol's stimulation of D1 proteasomal degradation [57]. Resveratrol also lowered the expression of cyclin B1 in five tumor cell lines. The extract triggered p21 production in all however, amongst the three intestinal cancer cell cultures it was used to arrest cell cycle in the S and G2 phases; in two other cell cultures, it resulted in G1 phase cell cycle arrest [58,59]. Variations in proteins transcription in various cell lines are undoubtedly related to these variances in polyphenols impact on proteins involved in cell cycle control [60,61].

5. Applications of polyphenols in colorectal tumor treatment

Numerous signaling pathways, including the NF-κB pathway, MAPK pathway, PI3K/AKT pathway, Wnt/β-catenin pathway, and c-Jun N-terminal kinase (JNK) pathway, are modulated by polyphenols both in vitro and in vivo, as recent studies have shown. These modulations have therapeutic and preventive effects against colon cancer [62,63]. Curcumin decreased the protein expression of NF-κB, cJNK, protein tyrosine kinases, and protein serine/threonine kinases (GSK-3β), further suppressing carcinogenesis, as demonstrated by previous research that also revealed curcumin lowered the expression of COX-2, iNOS, and TNF genes [64]. To alleviate colon cancer, cocoa polyphenols also reduced the expression of pro-inflammatory enzymes like nitric oxide (NO) synthase and the inflammatory marker COX-2. They also inhibited NF-κB nuclear translocation and JNK phosphorylation [64]. On the other hand, in human cancer colon fibroblast cells, gallic acid equivalent (GAE) therapy improved intracellular ROS generation and decreased the expression levels of TNF-α, IL-1β, IL-6, and NF-κB to restrict cell proliferation [65]. Based on these findings, polyphenols may be important in preventing colon cancer by influencing the inflammatory cytokine generation, immune cell activation, and important signaling pathways that control the inflammatory tumor microenvironment [66].

5.1. (−) Epigallocatechin -3-gallate

The main catechin in green tea is the molecule (−)-epigallocatechin-3-gallate (EGCG). Many tumor cells in humans experienced halt in cell cycle due to epigallocatechin-3gallate. Cell cycle arrest typically happened at G1 (Fig. 5). Cell cycle in G1 of cancer cells is inhibited by EGCG in pancrease through controlling the manifestation of cyclin D1, and CKD inhibitors p21 and p27. The guardian of the genome 'the p53 protein' is transcriptionally targeted to p21. Cell cycle arrest is triggered by its activation in normal cells upon the appearance of DNA damage [67,68]. It is particularly significant that EGCG activates p21 and that cell cycle arrest happens in the absence of p53 gene because the p53 gene is absent in many cancers [52,60,61].

5.2. Apigenin

Apigenin, also known as 4′,7-trihydroxyflavone, is a naturally occurring flavone family chemical present in numerous plants. It functions as the aglycone of several naturally occurring glycosides [69]. Celery, parsley, and other vegetables contain apigenin, which impedes cancer cell growth and rises the expression of p21 in a p53-independent way [52,69]. Furthermore, apigenin reduced the phosphorylation of pRb. In cells containing active p53, apigenin stabilized this protein by phosphorylating it at Ser15, which in turn facilitated cell cycle arrest through a p53-dependent pathway [52,69]. Apigenin appears to have multiple effects on cell cycle regulatory proteins, considering that it inhibited the transition of pancreatic carcinoma cells from the G2 phase to mitosis by lowering the levels of phosphorylated forms of CDK2, activator protein cdc25A, and cyclins B and A [52]. (Fig. 5).

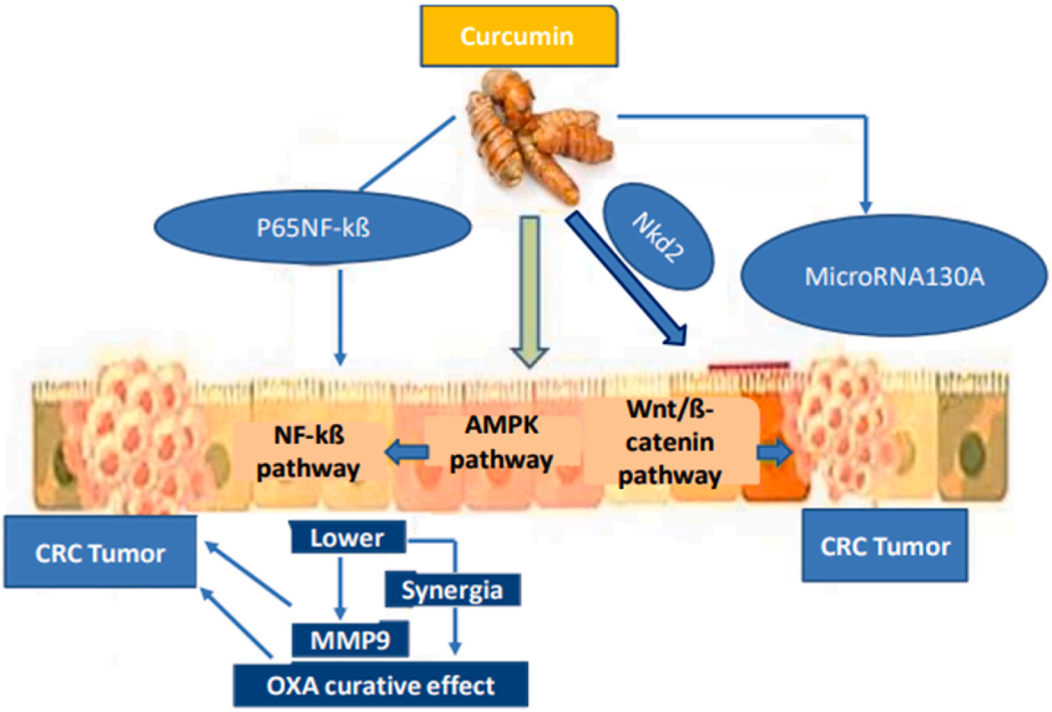

Fig. 6. Curcumin mechanism of action on CRC cells. Curcumin suppresses cell proliferation through the expression of Nkd2 which regulates the Wnt/β catenin pathway decreasing the expression of CRC tumor.

5.3. Silymarin and curcumin

Silymarin, a combination of flavonoids derived from milk thistle (*Silybum marianum*) that includes silybin, isosilybin, silychristin, silydianin, and taxifolin, has several known targets [70]. Silymarin inhibited cyclin D1 levels and elevated the inhibitory proteins p21, p27, and INK4a/15, causing cell cycle arrest at G1S transition. In prototypes of mouse treated with other tumor growth promoters, such as UV radiation, 7,12-dimethylbenz(*a*)anthracene, and phorbol 12-myristate 13acetate, silymarin was likewise active [71].

Curcuma longa yields a bioactive monomer called curcumin [72]. It has been demonstrated to possess anti-inflammatory, anti-oxidative, and anti-proliferative properties as a phytochemical agent. Curcumin's negative regulation of cyclin and CDK activity along with its upregulation of CDKI expression are connected to its growth inhibitory impact on numerous cancer cells in vitro [73] (Fig. 5). It is imperative to note that when investigating the anticancer's polyphenols impact in vivo through the usage of diverse tumor growth promoters, mutant mice, or xenograft animal models, the exact pathways responsible for these actions are often not clearly defined. Following the implantation of human cancer cells into immune-compromised animals, genistein, apigenin, and curcumin showed antiproliferative efficacy in xenograft animal models [52,73].

CRC development involves several signaling pathways, one of which is thought to be critical: the Wnt cascade [72]. Most CRC patients have mutated gene in Wnt signaling players, namely APC and β-catenin. The SW480 cell line's cell proliferation was inhibited by curcumin, which was linked to miRNA-130a downregulation and Wnt/β-catenin pathway inhibition. The anti-CRC curcumin activity is also influenced by miRNAs regulation. According to Ojo et al. [72], CRC cells inhibited by curcumin recovered when miRNA-130a was overexpressed. Enzyme-type plasminogen activator (uPA) and matrix metalloproteinase-9 (MMP9) regulate the invasion of cancer cells via activating AMPK and inhibiting NF-κB. Also, curcumin downregulated the expression of NF-κB, thus increasing the reactivity of drug-resistant colorectal cancer cells to oxaliplatin (OXA). Curcumin with OXA induced significant cell death and decreased colony development in comparison to curcumin or OXA [43] (Fig. 6). Weng and Goel [74] observed that animals exhibiting liver metastases originating from CRC cells showed reduced tumor growth with application of curcumin. According to Zhang et al. [43] and Ma et al. [75], clinical trial outcomes suggest that patients with metastatic CRC who receive oral curcumin in conjunction with chemotherapy may find it safe and well-tolerated.

5.4. Piperlongumine

The fruit of the long pepper (*Piper longum*) contains an amide alkaloid called piperlongumine (PPL) (5,6-dihydro1 - [(2E)-1-oxo-3-(3,4,5- trimethoxyphenyl)-2-propenyl]. Statistics indicate that PPL may have chemopreventive effects on malignancies of the mouth, breast, liver, kidney, stomach, pancreas, colon, and bladder and also lymphomas and melanoma [76]. Three mechanisms exist for PPL to function: activation of Suppressor of Mothers against Decapentaplegic family member 4 (SMAD4) pathway, reduction of antioxidant

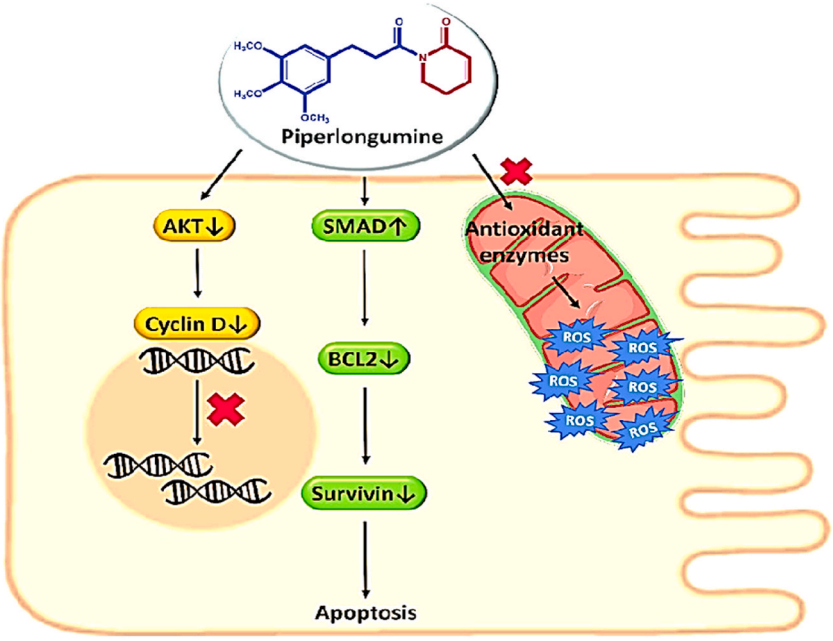

Fig. 7. Anticancer mechanism of piperlongumine in colon cancer Piperlongumine functions in three different ways: it inhibits the activity of antioxidant enzymes, which increases ROS levels; it blocks Akt activation; and it activates the SMAD4 pathway, which effectively triggers the death of cancer cells [76]. Symbols show activating (↑), inhibitory (↓) effects of some polyphenols.

enzyme activity and increase in ROS levels, and antimetastatic effect. PPL particularly boosts ROS production in cancerous cells. Cell death results from apoptosis, which is triggered by an excessive quantity of ROS. According to Kung et al. [77] and Rai et al. [76], PPL produces ROS, which subsequently inhibit Akt activation and cause cancer cells to die via the caspase- or Ras-mediated pathway. A different mechanism involves the overexpression of SMAD4, which raises the production of p21 (Senescence-inducing p21 is a critical cell cycle regulator). This results in the blocking of B-cell lymphoma 2 (BCL2) and the anti-apoptotic protein survivin, ultimately leading to apoptosis (Fig. 7). Thus, the colonic tumor-killing action of PPL is connected with the ROS/Ras/Akt and SMAD4 signaling pathways [77–79].

5.5. *Resveratrol*

Resveratrol is a compound that is obtained from grapes, peanuts, and mulberries. It has the prospective to inhibit cancer by acting on multiple signaling pathways, such as AMPK, ROS, NF-κB, and caspases [80]. Amongst the primary mechanisms of CRC is chronic inflammation. Anti-inflammatory substances may therefore be helpful in treating CRC. Damaged tissues rapidly release cytokines, which activate inflammatory response [81]. Previous research has demonstrated that intestinal cells uncovered to cytokines can activate inflammatory pathways such as JAK-STAT, NF-kB, and MAPK cascades; additionally, pro-inflammatory enzymes can be expressed more highly; pro-inflammatory mediators can be produced; and reactive oxygen species (ROS) can be produced [81–87]. Pro-inflammatory mediators including TNF-α and IL-1β, pro-inflammatory enzymes like iNOS and COX-2, and inflammatory signaling pathways like NF-kB are all reduced by resveratrol. Structurally analogous to resveratrol, pterostilbene (*trans*-3, 5-dimethoxy-4′-hydroxystilbene) suppresses the p38 MAPK signaling pathway, which in turn induces COX-2 and iNOS. This anti-inflammatory effect helps prevent colon cancer [83,87]. Furthermore, resveratrol is a profitable, non-toxic supplement and a different approach to reduce colitis and the strongly associated colon cancer. Resveratrol significantly raises the score for inflammation, lowers the number of neutrophils in the lamina propria and mesenteric lymph nodes, and controls CD3(+) T cells, which release TNF-α and IFN-γ. Additionally, observation indicated that resveratrol lowers the inflammatory marker P53 [84].

5.6. *Quercetin*

Onions, berries and asparagus are sources of quercetin, a flavonol molecule belonging to the flavonoid family [88]. Quercetin exhibits anti-CRC properties by modulating many molecular pathways involved in CRC. In CRC cells, quercetin-induced apoptotic events were linked to downregulation of the Wnt/β-catenin pathway and correlated genes (cyclin D1 and survivin) [88,89]. Quercetin may also have an inhibitory effect on CRC cells via regulating other pathways, including NF-κB, JNK/JUN, and PI3K/AKT/mTOR. A study carried out on mice in vivo shown that quercetin exhibited anti-CRC benefits by means of its anti-inflammatory characteristics. This resulted in a decrease in growth of tumor, a decline in inflammation, and a downregulation of markers associated with oxidative stress [88].

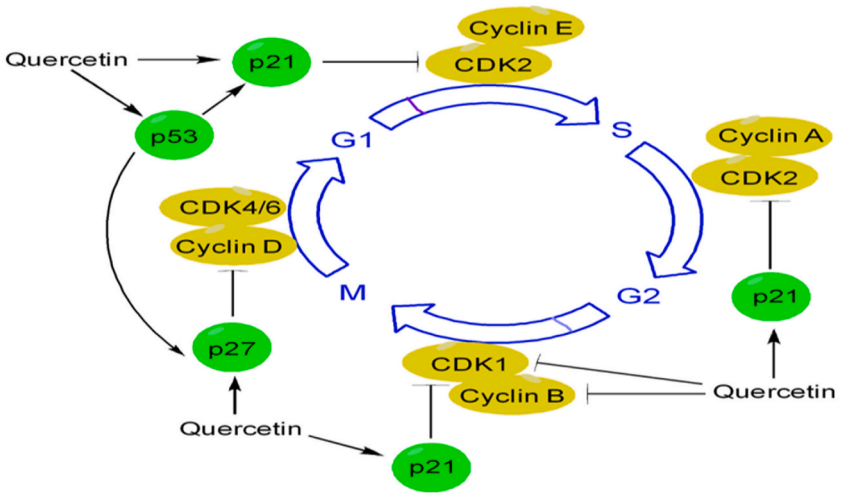

Fig. 8. Mechanism of quercetin-induced cell cycle arrest. Quercetin stimulates p21 to inhibit cyclin A (CDK2), cyclin B (CDK1) and cyclin E (CDK2) respectively. Quercetin also stimulates p27 to inhibit cyclin D (CDK4/6) [76]. Symbol show inhibitory (⊥) effects.

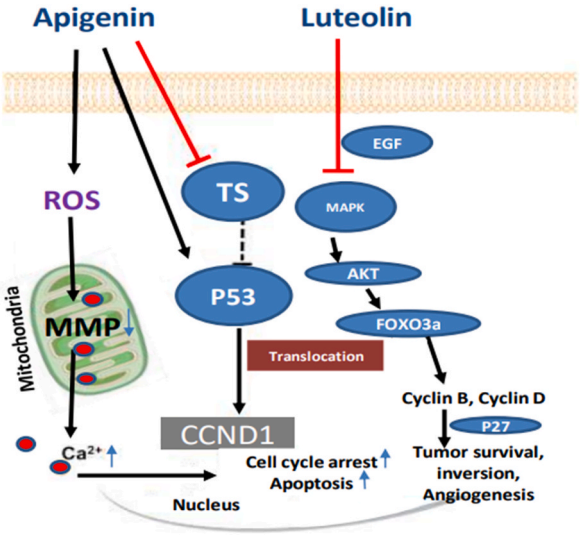

Fig. 9. The various ways that luteolin and apigenin inhibit colorectal cancer cells. Apigenin stimulate p53 and inhibits TS. Apigenin also causes the production of ROS and intracellular Ca^{2+} dysregulation leading to apoptosis. Luteolin inhibits MAPK through EGF.

Cell cycle advancement is fundamental in upholding cellular homeostasis, and its orderly progression relies on cyclins, cyclin-dependant kinases (CDKs), and CDK inhibitors (CDKIs) interaction [89]. Through its impacts on several target proteins, including p53, p21, p27, cyclin B, cyclin D, and cyclin-dependent kinases, quercetin encourages cell cycle arrest (Fig. 8). Quercetin preferentially induces p73 and p21 and inhibits cyclin B at the transcriptional and translational levels resulting in cell cycle arrest at the G2/M phase. According to Rather and Bhagat [88], quercetin can also downregulate cyclin B1 and cyclin-dependent kinase-1 (CDK-1), which are essential for the cell cycle's orderly passage through the G2/M phase. On the other hand, quercetin-induced cell arrest is not less frequent and is brought about by the increase of p21 and concurrent phosphorylation of retinoblastoma protein (pRb), that prevents the progression of G1/S cell cycle by obstructing transcription factor E2F1 [90]. Depending on the kind of cell, quercetin can stop growth of cells even in the G1 phase (Fig. 8).

Since quercetin interacts with several regulators, it can stop cancer cells growth at the G1, G1/S, or G2/M phases. For instance, it hinders cyclin D and rises the manifestation of p21, p27, and p53 to cause G1 growth arrest. Strong cyclin-dependent kinase inhibitor p21 specifically prevents the CDK2-cylcin E complex from being activated. This prevents CDK-dependent phosphorylation of pRb and attenuates E1F2, which in turn prevents transcription triggered by E2F1. In order to maintain an organized progression via S phase and G2/M, correspondingly, p21 also suppresses the activity of CDK2-cyclin A and CDK1-cyclin B. Cell cycle inhibitors like p21 and p27 are increased by quercetin-induced P53. P27 has several effects on the cell cycle. Specifically, G1 cell cycle arrest is brought on by p27's

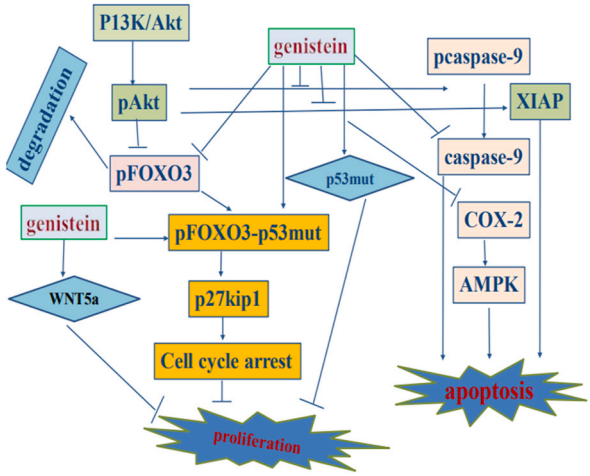

Fig. 10. Genistein inhibits proliferation in CRC cells by promoting FOXO3 activity. Genistein stimulates the connection between FOXO3 and p53 and inhibits PI3K/Akt, hence increasing FOXO3 activity. Further up the line, p27kip1 expression is elevated by genistein-mediated FOXO3 activity, which encourages cell cycle arrest and suppresses proliferation [100]. Symbol show inhibitory/suppressive (⊥) effects.

inhibition of CDK4- and CDK6-cyclin D complex activity [88].

5.7. Luteolin

Flavone is one class of flavonoid, which includes luteolin and apigenin. Their efforts to combat CRC exhibit certain parallels (Fig. 9). Report shows that apigenin inhibits the relocation and explosion of CRC cells through upregulating transgelin expression and downregulating the countenance of MMP-9, which is facilitated by Akt pathway [43]. MMP-9 is repressed by transgelin. In another study, apigenin was shown to reduce NEDD9 expression, which in turn blocked the Akt pathway and allowed CRC cells to penetrate and migrate. Additionally, by blocking the NF-κB/Snail pathway, apigenin interfered with CRC cell migration via inhibiting EMT [91].

Tumor necrosis factor (TNF)-alpha has been shown to be sensitized by luteolin, which causes CRC cells to undergo apoptosis by suppressing NF-κB and the genes it targets [92]. It was discovered by Pandurangan and associates that luteolin caused colon cancer cells to enter a cell cycle arrest and eventually die. Glycogen synthase kinase-3β and cyclin D1 controlled this process through the Wnt/β-catenin pathway [93]. They showed proof of additional mechanisms behind luteolin's anti-CRC effects in a mouse model of CRC caused by azoxymethane (AOM). By having an antioxidant impact on the cell membrane glycoprotein, luteolin decreased pre-neoplastic lesions and hindered growth of tumors. After luteolin supplementation, mice's expression of the tumor markers MMP-9 and MMP-2 that spread to other areas of the body were inhibited, suggesting that luteolin has anti-metastatic effects against CRC [93]. The Nrf2 pathway was activated by luteolin treatment, which slowed the growth of the tumor [93].

5.8. Anthocyanins

Anthocyanins are important members of flavonoid family that are extensively disseminated in different vegetables, fruits and wines [94]. Anthocyanin administration is connected with a decreased risk of CRC genesis, with respect to a recently available meta-analysis of seven observational studies [95]. Purple-fleshed potato anthocyanins reduced colonic CSCs' cell propagation and sphere formation; these processes were likewise controlled by the Wnt/β-catenin pathway [96]. A high anthocyanin content in strawberries reduced inflammation incidence, which in turn prevented colon cancers in mice by suppressing oncogenic pathways such as PI3K, ERK, and NF-κB [96]. According to signal transduction studies, delphinidin prevented phosphorylation of ERK at initial stages and JNK at late times, but not phosphorylation of p38 [96,97]. Moreover, c-Jun (a phosphorylation target of JNK and ERK), SAPK/ERK kinase (SEK, a JNK kinase), and MAPK/ERK kinase (MEK, an ERK kinase) are all inhibited by delphinidin. Delphinidin inhibits the JNK and ERK signaling pathways, which in turn suppresses TPA-induced AP-1 activity and cell transformation [95,96].

According to structural-activity relationships (SAR), the *ortho*-dihydroxyphenyl functional group on the B-ring of anthocyanidins is essential for blocking the action of AP-1 and cell transformation [96]. The compound also suppresses the apoptotic effects of caspases 3, 7, 8, and the mitochondrial related pathway (MAPK/ERK) to prompt apoptosis. Additionally, anthocyanins have demonstrated cyclin-B inhibition by interim on the p51 and p21 signaling pathways to encourage cell cycle arrest.

5.9. Genistein

Research has demonstrated that genistein inhibits the activation of PI3K/Akt., which prevents FOXO3 phosphorylation (inactivation) in CRC cells [98,99]. This also uncovered a novel method by which genistein reduces CRC cell proliferation (Fig. 10). Qi et al. [100] demonstrated that in colon cancer cells, genistein inhibits EGF-induced FOXO3 disassociation from the p27kip1 promoter, hence

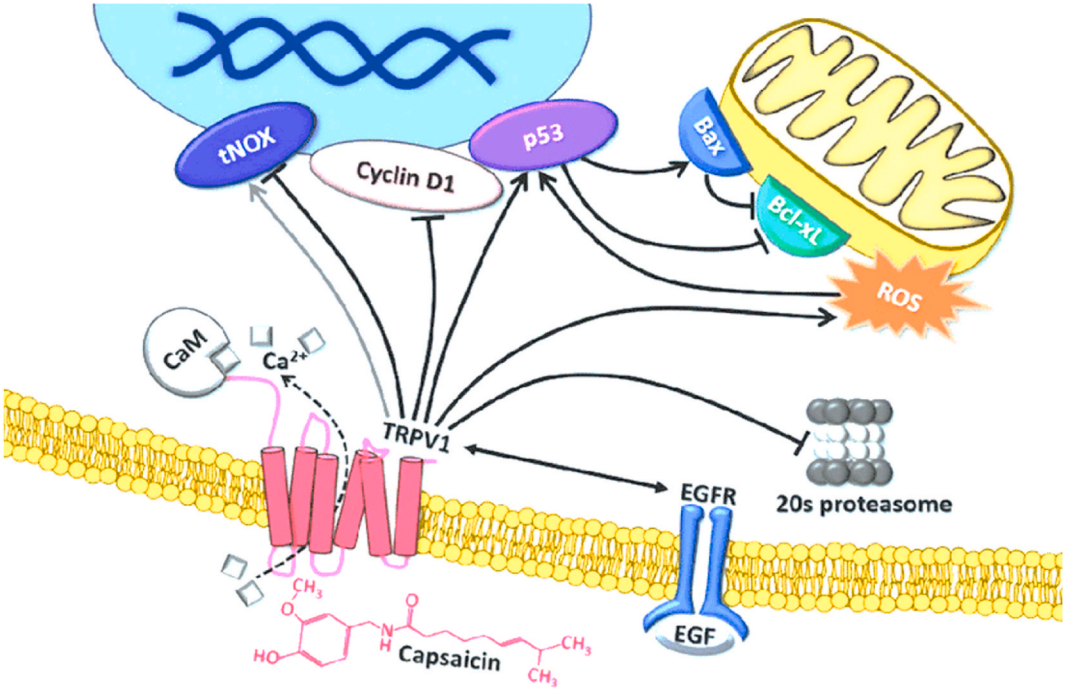

Fig. 11. Main mechanisms behind capsaicin antitumoral actions in colorectal cancer. A double arrow is used to illustrate the signaling feedbacks and inter-activations of TRPV1 and EGFR receptors. Capsaicin suppresses the activity 20s proteasome and Cyclin D1. tNOX, which is stimulated at low capsaicin concentrations and inhibited at higher concentrations, is another example of the dual dose-dependent impact. Capsaicin promotes p53 gene activation which stimulates Bax levels and suppresses Bcl-xL [107].

mitigating proliferation through ended expression of the cell cycle inhibitor p27kip1. Here, the author demonstrate that via encouraging FOXO3 binding to the p27kip1 promoter, genistein raises p27kip1 appearance in CRC cells. Genistein's anti-proliferative effects in breast cancer cells are accomplished by increased levels of the cell cycle inhibitor p27kip1 [101–103], but the underlying mechanisms are unknown. It is crucial to remember that the other molecules that are targeted also have an impact and that elevated p27kip1 caused by genistein is probably one of the contrivances of hang-up of proliferation. This study also showed that interaction between mutant tumor suppressor p53 and FOXO3 is necessary for enhanced p27kip1 expression. Qi et al. [100] showed that genistein raised wild type but not mutated p53 expression in human lung cancer cells, whereas it increased mutated p53 expression in colon cancer HT-29 cells [101–104]. Given the implication of p53 mutations on CRC development, genistein antiproliferative qualities may be linked to p53 targeting, which in turn stimulates FOXO3 action and cell cycle arrest [105,106]. According to Qi et al. [100], this study showed that genistein inhibits CRC cell development by decreasing the negative impact of EGF on tumor suppressor FOXO3 function. This, in turn, promotes FOXO3 interaction with mutant p53, which results in the production of p27kip1 and cell cycle arrest.

5.10. Capsaicin

Capsaicin, a foremost spicy component of chili peppers, is a subcategory of polyphenolic amides which are members of the polyphenol family. It has demonstrated chemopreventive properties against CRC [107]. The aptitude of TRPV1, a calcium-permeable ion channel, to be gated by extreme heat and specific related compounds from the vanilloids group is what makes it so famous [108–112]. It has remained highlighted that TRPV1 is expressed in intestinal epithelial cells, which have a close relationship with the EGFR pathways [113–115]. The EGF is in charge of cellular differentiation, growth, survival, motility, programmed death, and propagation [107]. TRPV1 is intrinsically activated in response to EGFR stimulation. Furthermore, inhibiting EGFR may prevent cancer cells from proliferating and developing since TRPV1 starts a direct negative feedback loop on EGFR. In contrast, absence of TRPV1 signaling causes hyperactivation of EGFR pathways, which may encourage cell proliferation and raise the threat of malignancies of the duodenal epithelium [107,116] (Fig. 11).

Capsaicin's signaling properties are displayed as both activating (arrowhead) and inhibitory (transverse bar). Besides raising protein levels through p53 gene activation, capsaicin encourages the creation of ROS. Bax and Bcl-xL levels are regulated by P53, which causes apoptosis. Tumor-associated NADH oxidase (tNOX), which is increased at little capsaicin quantities and repressed at greater concentrations, is another example of the twofold dose-dependent impact [107]. Cyclin D1 is degraded by capsaicin, and the 20s proteasome's activity is reduced. Summary of the mechanism of action and effects of different natural polyphenols in prevention of CRC are shown in Table 2.

Table 2
Role of different natural polyphenols in prevention of CRC.

S/N	Polyphenols	Mechanism of action	Effects	References
1	(−) Epigallocatechin -3-gallate	EGCG inhibits GRP78 expression, activates the NF-κB for HCT-116, and enhances miR-155-5p level.	EGCG exerted its greatest protective effects by blocking inflammatory responses, lowering oxidative stress, and reducing apoptosis	[117]
2	Apigenin	Suppressed CRC cell proliferation, migration, and invasion and intestinal organoid growth by inhibiting the Wnt/β-catenin signaling pathway	Apigenin inhibits cancer cell proliferation by triggering cell apoptosis, inducing autophagy and modulating the cell cycle. Apigenin also decreases cancer cell motility and inhibits cancer cell migration and invasion.	[118]
3	Silymarin and curcumin	Silymarin and curcumin induced apoptosis through the p53 pathway and the Wnt signaling pathway	Curcumin inhibited colon cancer cell proliferation in a concentration-dependent manner, whereas silymarin showed significant inhibition only at the highest concentrations assessed. There are synergistic effects when colon cancer cells were treated with curcumin and silymarin together.	[119]
4	Piperlongumine (PPL)	PPL produces ROS, which subsequently inhibit Akt activation and cause cancer cells to die via the caspase- or Ras-mediated pathway	It elevates cellular levels of reactive oxygen species (ROS) selectively in cancer cell lines	[78]
5	Resveratrol	Resveratrol decreases pro-inflammatory mediators, such as TNF-α and IL-1β, pro-inflammatory enzymes such as iNOS and COX-2 and inflammatory signaling pathways such as NF-kB	Resveratrol, in interaction with standard drugs, is an effective chemosensitizer for CRC cells to chemotherapeutic agents and thus prevents drug resistance by modulating multiple pathways, including angiogenesis, cell cycle, and apoptosis.	[120]
6	Quercetin	In colorectal cancer cell lines, researchers used TGF-β1 to induce Epithelial–mesenchymal transition (EMT) in cancer cells. Administration of quercetin can inhibit Twist1 and regulate E-cadherin expression to inhibit EMT	During the intrinsic apoptotic pathway, quercetin activates caspase-3, -8, -9, stimulates the expression of Bax, Bad and down-regulates the anti-apoptotic proteins, such as Bcl-XL, Bcl-2 and Mcl-1.	[121]
7	Luteolin	Luteolin inhibits the MAPK signalling pathway in CRC cells.	By inducing apoptosis, initiating cell cycle arrest, and decreasing angiogenesis, metastasis, and cell proliferation	[122]
8	Anthocyanins	Anthocyanins avoid metastasis and inhibit cell growth by acting on Ras-MAPK and PI3K/Akt signal cascade pathways	Anthocyanins can act indirectly or directly by targeting multiple signaling pathways leading to CRC development, therefore inducing apoptosis and cell cycle arrest, and blocking cell migration, metastasis, and uncontrolled inflammation and oxidative stress.	[123]
9	Genistein	inhibit colon cancer via the PI3K/Akt pathway	Genistein exerts potential antimetastatic CRC benefits, presumably by blocking the PI3K/Akt in CRC cells through a molecular mechanism	[124]
10	Capsaicin	The TRVP1 agonist capsaicin inhibit CRC growth by activating P53	Overexpression of TRPV1 by capsaicin treatment could inhibit cell and increase cell apoptosis in HCT116 cells through activating p53.	[62]

6. Polyphenols delivery system

Phenols show considerable promise in both cancer treatment and prevention. However, their potential application as medicines is limited by their abridged solubility and steadiness. To stop the precipitation, quick breakdown, and bioactive substances clearance and bioavailability increase, it has been stressed that delivery outfits that can get beyond significant obstacles must be developed [56]. Pimentel-Moral et al. [125] state that nanoformulation takes advantage of the differences amongst cancer cells and ordinary cells inside the tissue to achieve huge loading competence, protection, and targeted delivery. The features of numerous polyphenol-loaded nanoparticles (Fig. 12) and their anticancer possessions are reviewed in this section.

Low water solubility polyphenols are most frequently entrapped using lipid-based formulations. For competent drug distribution, lipid nanoparticles can recover polyphenols stability, and biocompatibility. Liposomes, phytosomes, emulsions, and nanoparticles are illustrations of formulations that are frequently employed [125].

Liposomal delivery is the greatest well-known application of nanoparticles. Their primary constituent, phospholipids, amphipathic nature let them to form nanoparticles through a bilayer structure that mimics a cell membrane [126]. The hydrophilic liposome core allows the liposome to be packed with substances that dissolve in water, while the hydrophobic liposome membrane protects the polyphenols from the external environment [125,127].

In order to create nanoparticles, scientists are trying to construct DDSs from amphiphilic materials such as phospholipids and biocompatible solid or liquid lipids. High stability, controlled release, targeted administration through surface modification, and high encapsulation efficiency are just a few advantages that come with using nanostructured lipid particles (NLPs) [128]. Kanwal et al. [129] created a self-nanoemulsion to produce curcumin by using sodium N-[8-(2-hydroxybenzoyl) amino]caprylate (SNAC), an absorption enhancer. According to Kanwal et al. [129] the SNAC absorption enhancer is an excellent oral administration technique for increasing curcumin oral bioavailability and cell absorption.

Natural polymers can be found as hydrogels, films, meshes, and nanoparticles, among other forms, in a wide range of applications.

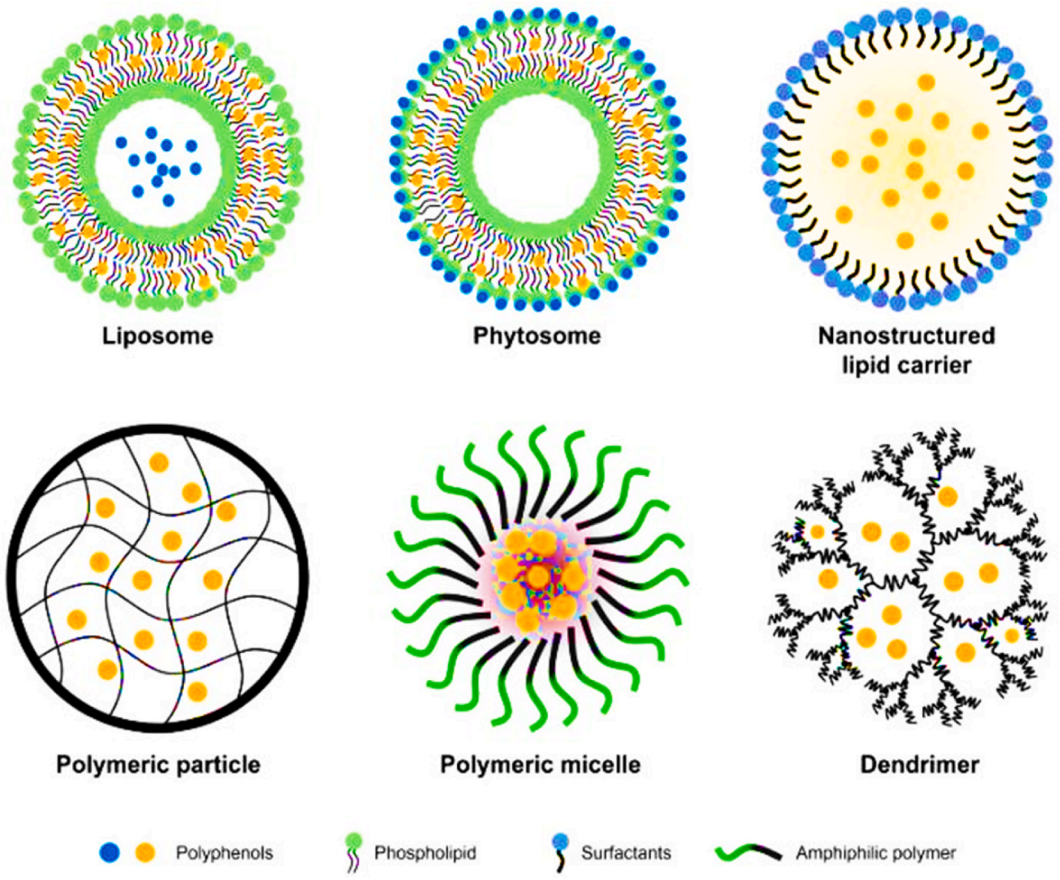

Fig. 12. Typical natural polyphenol medication delivery systems.
Source: Kim et al. [56].

Depending on the drug or target, polymers can be chosen based on their different architectures, charges, heat stability, and pH sensitivity [130]. Hydrophilic or hydrophobic polyphenols can be loaded onto polymer nanoparticles, and their size and surface area allow for selective distribution [56,130,131]. One naturally occurring polymer that is frequently used to administer medications is chitosan. FA is a water-soluble B vitamin whose receptors are overexpressed on the surface of cancer cells, according to Tagde and colleagues [130]. This makes it a popular target for drug delivery. Mary Lazer et al. [132] treated cancer cells with the flavonoid hesperetin using the chitosan-FA combination. The hesperetin-chitosan conjugate nanoparticles (CFH NPs) had an enhanced absorption and retention effect, which allowed them to diffuse to cancer cells at a particle size of 457 nm. Compared to non-FA conjugated nanoparticles, the particles' cellular absorption was three times more and their encapsulation efficacy was 98 % higher [133].

A dendrimer is a nanoparticle having a branching polymer, according to Ma et al. [131], Ben-Zichri et al. [134] co-formed curcumin and resveratrol using dendritic polymer nanoparticles. The polyphenols (resveratrol and curcumin) contained within a dendrimer of 130 nm in size shown a noteworthy decrease in light-induced degradation, suggesting the nanoparticles resilience. Targeting the mitochondria of human-derived SH-SY5Y cancer cell line, the resveratrol/curcumin dendrimer produces cytotoxicity. A decrease in cytochrome C oxidase activity, an increase in intracellular calcium release, and a depolarization of the mitochondrial membrane were the results of the mechanistically focused action of these nanoparticles, according to Ben-Zichri et al. [134].

It is possible to combine hydrophobic and hydrophilic polymers to create micelles. Ma et al. [131] co-encapsulated doxorubicin (DOX) and curcumin using polymeric micelles (PMs) of hyaluronic acid-vitamin E succinate (HA-VES). The PMs showed an impressive encapsulation efficacy of 72 % for curcumin and 94 % for DOX. Their uniform size was 223 nm. The cancer cells MCF-7/Adr are resistant to DOX and overexpress P-glycoprotein (P-gp), a transporter that facilitates medication efflux. These PMs were 14.83 times more cytotoxic in MCF-7/Adr cells than free DOX, which makes sense as curcumin inhibits P-gp and micelle encapsulation increases its stability [131].

Animals and plants include proteins, which are naturally occurring polymers that have minimal toxicity and can be employed as stable drug distribution medium [22]. Notwithstanding of the kind of polyphenol, proteins' amphiphilic character can enhance solubility and constancy. According to Kashyap et al. [22], proteins can also combine with polyphenols to create biocompatible nanoparticles that have a great conveying capacity. Furthermore, Jain et al. [135] have reported that protein nanoparticles with modified surfaces can readily alter their functional groups or incorporate extra defensive covers for efficient formation. Suktham et al. [136]

Table 3
Summarizing of drug delivery systems for polyphenols.

	Polyphenols	Drug delivery systems	References
1.	(−)Epigallocatechin -3-gallate	EGCG can be delivered to tumor tissues using a variety of nanomaterials, such as protein nanoassemblies, chitosan nanoparticles, mesoporous silica nanostructures, gold nanoparticles, and lipid nanoparticles.	[137]
2.	Apigenin	β-cyclodextrin: Apigenin is formulated as nanocrystal using supercritical fluid, self-microemulsifying drug delivery system, complexation with β-cyclodextrin	[138]
3.	Silymarin and curcumin	Albumin nanoparticles: In vitro COVID-19 experiment and oleic acid-induced lung damage, silymarin/ curcumin-loaded albumin nanoparticles coated with chitosan were observed to exhibit anti-inflammatory and anti-COVID-19 properties.	[139]
4.	Piperlongumine	Chitosan: Chitosan nanoparticles (CsNPs) are a potential class of drug carriers that carry piperlongumine safely and effectively while effectively mediating anticancer action.	[139]
5.	Resveratrol	Liposomes: Resveratrol-loaded liposomes showed better drug release (100 %) over a 24 h period likened to free resveratrol	[140]
6.	Quercetin	Applications of delivery systems technologies, including hydrogels, solid dispersions, phospholipid complexes, encapsulation, and microparticle delivery systems, can increase the bioavailability of quercetin.	[141]
7.	Luteolin	A nano-composite carrier, NH_2-MIL-101(Fe)@GO (MG), based on aminated MIL-101(Fe) and graphene oxide (GO) for luteolin has been established and evaluated delivery systems for targeted treatment methods for colorectal cancer.	[142]
8.	Anthocyanins	Halloysite nanotubes (HNT) loaded with anthocyanins are proposed as a potentially effective pH-responsive drug delivery mechanism for the treatment of colorectal cancer.	[143]
9.	Genistein	Bacterial nanocellulose: The adsorption of genistein is increased by genistein drug delivery systems based on bacterial nanocellulose.	[144]
10.	Capsaicin	Designed lactoferrin (LF) decorated nanosystem for targeted delivery of capsaicin (CAP) in colorectal cancer cells. CAP-loaded egg albumin nanoconjugates with LF functionalized carboxymethyl dextran (CMD) coating have been developed. The LF decoration on LF-CMD@CAP-EGA-NCs provided sustained delivery of CAP.	[145]

used sericin nanoparticles to distribute resveratrol. Protein particles with an encapsulation efficiency of 71–75 % and a size range of 200–350 nm were extremely biocompatible. Table 3 highlights some drug delivery systems for polyphenols.

7. Conclusions

One of the main cancers that continue as a major problem to the general public and a hazard to community health worldwide is CRC. To change the situation, effective natural treatment strategy are desperately needed. According to this study, more and more naturally occurring polyphenols with notable anti-cancer properties are continually used to treat CRC. These polyphenols have anti-cancer properties through controlling CSCs and gut microbiota together with suppressing CRC cell growth and encouraging its death by controlling a number of chemicals and communication pathways. Notably, some polyphenols have better anti-cancer effects than others, and patients may benefit more from combining them with other plant-based chemicals in anticancer medications. Nevertheless one should not overlook constraints like low biological activity and stability. Consequently, in order to prolong their half-life in the body and encourage the creation of novel anti-CRC medications derived from natural polyphenols that will be of value to all of humanity, more potent biochemical preparations and distribution schemes, such as lipid-based formulations, liposomes, phytosomes, emulsions, and nanoparticles, are required.

CRediT authorship contribution statement

Joel Okpoghono: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization. **Endurance F. Isoje:** Writing – original draft, Methodology, Data curation. **Ufuoma A. Igbuku:** Validation, Data curation. **Ovigueroye Ekayoda:** Software, Project administration. **Godson O. Omoike:** Resources, Project administration. **Treasure O. Adonor:** Resources, Project administration. **Udoka B. Igue:** Writing – review & editing, Validation, Resources. **Solomon U. Okom:** Software, Project administration. **Faith O. Ovowa:** Resources, Project administration. **Queen O. Stephen-Onojedje:** Writing – review & editing, Validation, Resources. **Ejiro O. Ejueyitsi:** Writing – review & editing, Validation, Resources. **Anita A. Seigha:** Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Note applicable.

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