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Review article

Therapeutic opportunities in colon cancer: Focus on phosphodiesterase inhibitors

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ABSTRACT

Despite novel technologies, colon cancer remains undiagnosed and 25% of patients are diagnosed with metastatic colon cancer. Resistant to chemotherapeutic agents is one of the major problems associated with treating colon cancer which creates the need to develop novel agents targeting towards newer targets. A phosphodiesterase is a group of isoenzyme, which, hydrolyze cyclic nucleotides and thereby lowers intracellular levels of cAMP and cGMP leading to tumorigenic effects. Many *in vitro* and *in vivo* studies have confirmed increased PDE expression in different types of cancers including colon cancer. cAMP-specific PDE inhibitors increase intracellular cAMP that leads to activation of effector molecules-cAMP-dependent protein kinase A, exchange protein activated by cAMP and cAMP gated ion channels. These molecules regulate cellular responses and exert its anticancer role through different mechanisms including apoptosis, inhibition of angiogenesis, upregulating tumor suppressor genes and suppressing oncogenes. On the other hand, cGMP specific PDE inhibitors exhibit anticancer effects through cGMP dependent protein kinase and cGMP dependent cation channels. Elevation in cGMP works through activation of caspases, suppression of Wnt/b-catenin pathway and TCF transcription leading to inhibition of CDK and survivin. These studies point out towards the fact that PDE inhibition is associated with anti-proliferative, anti-apoptotic and anti-angiogenic pathways involved in its anticancer effects in colon cancer. Thus, inhibition of PDE enzymes can be used as a novel approach to treat colon cancer. This review will focus on cAMP and cGMP signaling pathways leading to tumorigenesis and the use of PDE inhibitors in colon cancer.

1. Introduction

Colon cancer is a major clinical problem and the third leading cause of cancer worldwide. It is the second leading cause of cancer deaths in the U.S. population which represents 8.1% of all new cancer cases and 8.3% of all cancer deaths in 2018 [1]. In 2018, estimated new cases and deaths were 140,250 and 50,630 respectively [1]. Prevalence of colon cancer in men is 30% higher than in women and 40% higher the mortality ratio in men. The lifetime risk of developing colon cancer is approximately 1 in 21 (4.6%) for men and 1 in 23 (4.2%) for women [2]. In India, it is the fourth most common cause of cancer in men and the third most common cause in women. The age-standardized rate for developing colon cancer is 3.2 per 100,000 men and 5.1 per 100,000 women. However, the survival rate is lower in developing countries due to limited resources and inadequate health infrastructure. Five-year survival rate (2008–2014) is < 40% in India whereas in the U.S. it is 64.5% [3].

Colon cancer is an old age disease which occurs at the fifth decade of lifespan. Studies showed that 5–15% of the young populations are diagnosed with colon cancer which can be associated with inflammatory bowel disease or hereditary polyposis formation [4]. Other than age, sex, race/ethnicity, genetic makeup, history of CRC, dietary factors, increased BMI, red meat intake, low physical activity, long term cigarette smoking (30–40 years), low vegetables and fruit consumption is associated with colon cancer development [5].

With the development of newer screening techniques, early diagnosis of colon cancer is possible. Most of the patients undergo surgical resection after diagnosis. The problem associated with resection is that it reoccurs in a short time of about two years. In surgically resected patients, 60% of patients develop relapses in the first 2 years whereas 90% after the first 4 years [6–8]. Despite novel technologies for early diagnosis, > 25% of patients are diagnosed with metastatic cancer for which systemic therapy remains the treatment option. The cytotoxic agents and molecular targeted therapies like inhibitors of VEGF, tyrosine kinase, EGFR, BRAF, KRAS, MET and aurora kinase are used as chemotherapy and immunotherapy is being used as adjuvant or

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Table 1
Pharmacological therapy for colon cancer.

Treatment	Anticancer agent(s)
First line	5-Fluorouracil/leucovorin
	Capecitabine
	Bevacizumab/capecitabine
	Folinic acid, fluorouracil and oxaliplatin/oxaplatin and capecitabine
	Folinic acid, fluorouracil and irinotecan
	Folinic acid, fluorouracil and oxaliplatin/penitumumab
	Oxaplatin and capecitabine/cetuximab
Second line	5-Fluorouracil/oxaliplatin/capecitabine
	Cetuximab
	Bevacizumab
	Aflibercept
Third line	Cetuximab/irinotecan
	Penitumumab
	Regorafenib
	Trifluridine

palliative therapy [9]. List of current chemotherapeutic agents for colon cancer are provided in Table 1. Currently, the problem associated with treating colon cancer using chemotherapy is resistance to these agents. Most of the metastatic cancer develops resistance to adjuvant therapy in 3–12 months. Resistant to first-line therapies like 5-FU, capecitabine, irinotecan, and other chemotherapeutic agents creates a need for the development of more effective alternative therapies [10,11]. These points emphasize the need to develop novel agents targeting newer targets.

Phosphodiesterases (PDEs) are a group of isoenzymes that catalyze the hydrolysis of 3′ cyclic phosphate bond of cyclic nucleotides: cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [12]. PDE enzymes with 11 enzyme families and 50 isoforms have been discovered from which, each has different location and role in different diseases [13]. Non-selective PDE inhibitors like caffeine and theophylline have been used for respiratory disorders like asthma and airway diseases as a bronchodilator. Milrinone, a selective PDE3 inhibitor was developed for heart failure [14]. Recently approved roflumilast and cilomilast are potent PDE4 inhibitors used for treating COPD [15,16]. Other PDE4 inhibitors like rolipram and theophylline have been used as an antidepressant [17] and anti-asthmatic agents respectively [18]. Selective PDE 5 inhibitors sildenafil causes NO-induced relaxation that is used for erectile dysfunction [19] and zaprinast is used as mast cell stabilizer in allergic conditions [20].

Studies have reported high expression of PDE in many tumors such as prostate and testicular cancer [21,22], breast cancer [23], lung cancer [24–26], urinary bladder tumors [27,28] including colon cancer [29]. Moreover, the hydrolytic effect of PDE leads to a decrease in the intracellular level of cyclic nucleotides. A decrease in cAMP and cGMP

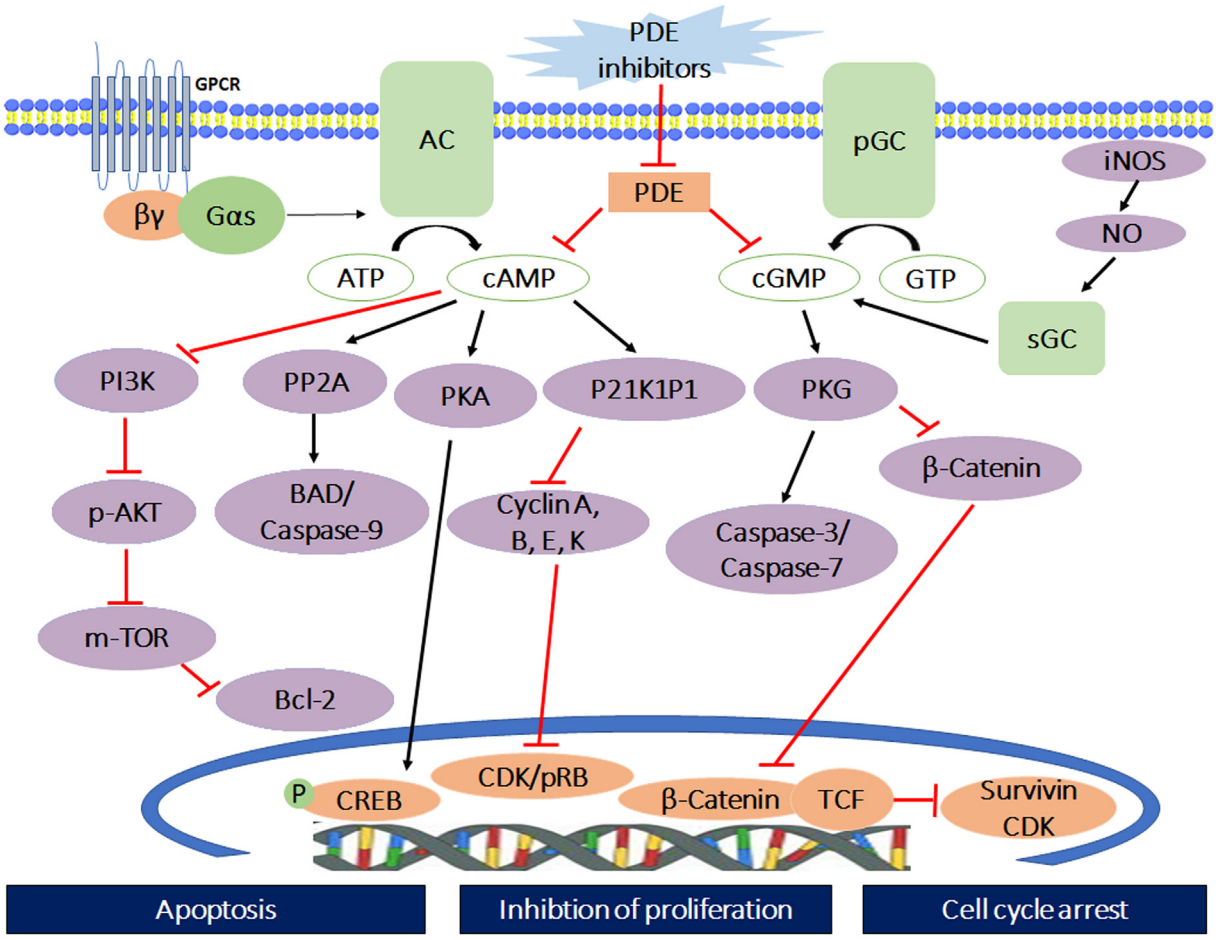

Fig. 1. cAMP is synthesized from ATP by the catalytic action of AC and cGMP is synthesized similarly from GTP by the catalytic action of pGC and sGC. PDEs hydrolyze cAMP and cGMP in 5′AMP and 5′GMP respectively. PDE inhibitors increase level of cyclic nucleotides which leads to activation of downstream pathways that leads to apoptosis, anti-proliferative and cell cycle arrest of colon cancer cells.
GPCR: G protein coupled receptor; AC: adenylate cyclase; pGC: guanyl cyclase; sGC: soluble guanyl cyclase; PDE: phosphodiesterase; cAMP: cyclic adenosine monophosphate; ATP: adenosine tri-phosphate; cGMP: cyclic guanosine monophosphate; GTP: guanosine tri-phosphate; iNOS: nitric oxide synthase; NO: nitric oxide; PKA: protein kinase A; PKG: protein kinase G; PI3K: phosphoionositide-3-phosphate; pAkt: phosphorylated Akt; PPA2: protein phosphatase 2; BAD: Bcl-2 agonist of cell death; CREB: cAMP response element binding protein; CDK: cyclin dependent kinase; TCF: T cell factor.

level has also been reported to have tumorigenic effects in several cancers [29]. Inhibition of PDE5 in non-small cell lung cancer has shown to have a cytotoxic effect [24–26]. Exisulind (PDE5 inhibitor) in combination with docetaxel had significantly reduced the tumor in orthotropic non-small cell lung cancer model [24–26]. Inhibition of PDE4D is associated with prostate cancer cell death and apoptosis in a nude mouse model [30]. Moreover, inhibition of PDE enzyme is reported to have anti-cancer effects in colon cancer [31], lung cancer [32], gastrointestinal stromal tumors [33], prostate cancer [34], glioma [35], leukemia [36] and ovarian cancer [37]. This review will focus on cAMP and cGMP signaling pathways leading to tumorigenesis and use of different PDE inhibitors in colon cancer.

2. Adenylate cyclase-cAMP pathway

Cyclic nucleotides, cAMP and cGMP are important second messengers in intracellular and extracellular signal transduction [38]. Intracellular regulation of cAMP is controlled by two different enzymes *i.e.* adenylate cyclase (AC) and PDE. cAMP is synthesized from ATP by the catalytic action of AC. PDE has the opposite action of AC that cleaves cAMP and regulates its intracellular concentration. PDE activation requires magnesium ions and it can be inhibited by selective or non-selective PDE inhibitors [39,40]. AC is stimulated by adrenergic agonists which release $G\alpha_s$ subunit of GPCR receptor protein that binds to AC. Production of cAMP leads to different cellular functions like gene expression, cell proliferation, growth, differentiation, cell cycle regulation, immune function, and metabolism according to its localization, cell type and stimulus to its signal [38,41–44] (Fig. 1).

2.1. cAMP in colon cancer

cAMP is a ubiquitous second messenger and its activation is further associated with the activation of cAMP-dependent protein kinase A (PKA-I and PKA-II). Two isoenzymes after binding with cAMP lead to the release of catalytic subunit serine-threonine kinase and phosphorylate downstream target molecules by which many cellular activities take place [45,46].

cAMP plays a major role in cell proliferation, apoptosis and cell cycle regulation in many tumor cells. Agents that induce cAMP activation are AC activators like forskolin, PDE inhibitors (selective and non-selective inhibitors) and cAMP analogs like 8-chloro cAMP, 8-bromo cAMP, and other derivatives. These agents work through different mechanisms involving cAMP signaling in cancer [47–52]. Elevation of cAMP can be a promising approach for cancer therapy. cAMP works through three main effectors: Protein kinase A (PKA), exchange protein activated by cAMP (EPAC) and cAMP gated ion channels which regulate cellular responses like apoptosis, proliferation, differentiation, vasodilation, and inflammation [53]. cAMP-mediated activation of PKA leads to cell cycle arrest and growth inhibition by apoptotic pathways in many cancer cells. Cyclic cAMP analog 8-bromo cAMP is supposed to activate PKA-II for growth inhibition in cancer cells [52,54]. Other approaches by which cAMP is involved in growth inhibition are blocking extracellular signal-regulated kinase (ERK) [52]; suppression of anti-apoptotic proteins Bcl2 and BclXI, upregulation of tumor suppressor gene p53 and suppression of oncogenes myc and erbB-2 [52,55,56]. Also, regulation of angiogenetic pathway by inhibition of VEGF, TGF-β, and EGFR is associated with elevation of cAMP levels. Many tumors show a lower level of cAMP and thus cAMP levels can be modified by activation of adenylate cyclase or inhibition of cAMP-specific PDE enzymes in tumor cells [57–60].

In vitro study in different colon cancer cell lines HT29, LIM 1215 and COLO 206F treated with cAMP analogs theophylline, 8-bromo cAMP, dibutyryl-cAMP and chlorophenylthio-cAMP revealed different effects on cancer cells. Former two analogs have shown to inhibit cancer cell growth while later two have an increased number of cells in colon cancer cell lines. These results make difficulty in understanding of cAMP role in colon cancer cell growth [61]. Variable results among these analogs can be as a part of the difference in their functional groups which are associated with different influence on cAMP [62]. These *in vitro* findings have confirmed the role of cAMP in the treatment of colon cancer. However, further preclinical and clinical studies are required to confirm the role of cAMP and its analogs for their beneficial effects in colon cancer.

2.1.1. Adenylate cyclase in colon cancer

Adenyl cyclase is an enzyme found in the plasma membrane and responsible for the synthesis of cAMP, a second messenger which plays an important role in various cellular reactions. It catalyzes the conversion of ATP to cyclic AMP and pyrophosphates in the plasma membrane [63]. It is a glycoprotein and is consisting of a large family of nine isoforms (AC I to IX) and each is encoded with separate genes (ADCY1 to ADCY9). It regulates its effects *via* GPCR (G-protein coupled receptor). G_i and G_s decrease and increase the level of AC respectively; moreover, forskolin, adenosine, and some hormones also regulate the stimulation of AC [64]. Catecholamines binding with β-adrenergic receptors or peptide hormones binding to their receptors stimulate AC activity. Accumulation of intracellular cAMP is dependent on these hormones. cAMP synthesized will travel from the plasma membrane to cytosol and binds to PKA to activate them. Activation of PKA will regulate various cellular metabolic reactions depending upon cell type [63].

AC activity is associated with many cancers as in ovarian cancer [65], colon cancer [66,67], gastric cancer [68], prostate cancer [69] and breast cancer [70]. Human colon cancer cell lines Colo 205 and WiDr, dermal fibroblast and cells cultured from colonic adenomas and colonic epithelium were evaluated to quantify and differentiate the level of AC and cAMP in benign cells and colon cancer cells [67]. Cholera toxin and EGF were used to measure the level of cAMP stimulation in these cells. This showed lower AC and cAMP activity in colon cancer cell lines compared to dermal fibroblast. Also, the authors reported that the difference observed in the level of cAMP was not because of PDE enzyme as in break down site but from the synthesis site. These can be useful in the differentiation of benign cells and malignant cells in colon cancer [67].

Adenyl cyclase activator forskolin has shown to inhibit the growth of chemoresistant KM12C colon cancer cells. Low level of forskolin inhibited proliferation and induced apoptosis by elevation of cAMP and subsequent suppression of Akt/protein kinase-B pathway [66]. In another study, forskolin is stated to inhibit proliferation of HT29 colon cancer cells. Forskolin and vasoactive intestinal peptide (VIP) suppressed the fetal calf serum (FCS) or insulin-induced proliferation in HT29 cells through the increasing level of cAMP [71]. They arrested the cell cycle in the $G0/G_1$ phase. Combination of forskolin and VIP showed a synergistic effect on proliferation and cAMP accumulation. This concludes elevation of cAMP induces cell cycle arrest at late G_1 or G_1/S transition [71].

Increase in cAMP levels is associated with either tumor cell growth or inhibition depending upon different cell types. Some of the studies are showing contrast results involved with adenyl cyclase expression [72]. ADCY9 gene is a member of AC gene family which is involved in a similar action as that of other AC enzyme families to produce cAMP from activation of GPCR. Mutation in ADCY9 gene is involved in the development of colon cancer. Colon cancer tissue samples were collected from patients and evaluated for the expression level of ADCY9 gene and clinical pathological features associated with it. Prolonged survival was observed in patients with lower expression of ADCY9 gene which results are contrasted with cAMP inhibitory effects on colon cancer [72]. Also, in prostate cancer cells expression of AC found to be higher and leading to the proliferation of tumor cells and inhibition of apoptosis. The possible mechanism was found to be EPAC/RAP/B-Raf signaling [73]. This summarizes the role of AC can differ in types of cells and activation of downstream signaling pathways in cancer cells.

Since many studies have shown beneficial effects of AC in colon cancer, activation of AC may have inhibitory effects in colon cancer through an elevation in the level of cAMP.

3. GC-cGMP pathway

Cyclic guanosine 3′, 5′-monophosphate (cGMP) is a cyclic nucleotide which is synthesized by the catalytic action of guanyl cyclase (GC). cGMP is synthesized from divalent metal bound GTP with the presence of divalent metal bound cofactor Mg^{+2} [74,75]. GC is evenly distributed between cytosol and membrane which is activated by direct stimuli. Ligands which activate GC are small paracrine peptides like guanylin, enterotoxins and some cytokines, natriuretic peptides and nitric oxide (NO) [76]. Alike cAMP, cGMP is also hydrolyzed by PDEs. cGMP hydrolyzing PDEs are PDE 1, 2, 3, 5, 6, 9, 10 and 11 from which PDE 5, 6, and 9 being specific to cGMP [77]. cGMP signaling has a positive or negative effect on cell growth depending upon the type of cell or tissues.

3.1. cGMP in colon cancer

cGMP is ubiquitously present intracellular second messenger and involved in various cellular processes as like cell growth, ion channel conductance, apoptosis, cell mobility and contractility [78]. It is abundantly present in the cardiovascular system for which it is implicated in cardiovascular disorders. cGMP synthesis is carried out by GC and it exerts its effects through cGMP gated cation channels and cGMP dependent protein kinase (PKG) [78].

cGMP regulation is associated with many types of cancers including colorectal cancers, breast cancer [79–81], gastric cancers [207], melanoma [82] and ovarian cancer [83]. As mentioned before, cGMP is activated by NO and natriuretic peptides which leads to activation of its three main effectors: PKG, cGMP gated cation channels, and PDE. PKG leads to activation of downstream singling pathways leading to various cellular responses like cell growth and proliferation, apoptosis, host defense, neuronal transmission and vascular and platelet homeostasis [84–86]. Anticancer effects of cGMP are mainly associated with the activation of PKG and downstream effector pathways. PKG activation leading to cell growth inhibition and apoptotic signaling is mainly through Wnt/β-catenin pathway [87], NF-κB pathway [88] and increase in caspase levels [89]. Other approaches by which cGMP/PKG leading to inhibition of colon cancer cells are activation of caspase-3 and caspase-7 [90], suppression of β-catenin, T-cell transcriptional factor (TCF) transcription, cyclin D1, and survivin [91,92] and iNOS and INFγ pathway [91]. These studies have explained the inhibitory role of cGMP in colon cancer growth and proliferation through several distinct pathways, which can be further evaluated to confirm their role in treating colon cancer.

3.1.1. Guanyl cyclase in colon cancer

GC was the first enzyme which was found to be forming cyclic nucleotide (cGMP) [76]. It gets activated directly by ligand attachment to GC receptors [93,94]. GC is evenly distributed between membrane (pGC) and in the cytosol (sGC) [76]. Membrane-bound GC, also known as seven particulate GC differ in tissue distribution and ligand binding sensitivity and it responds to small natriuretic peptides, cytokines, guanylin and enterotoxins [76,93]. Whereas, soluble GC (sGC) located in the cytosol is activated by nitric oxide (NO) [76].

Soluble GC is divided into four subunits as α_1, α_2, β_1 and β_2 while pGC has seven subunits as GC-A, GC-B, GC-C, GC-D, GC-E, GC-F and GC-G [95]. Among these, GC-C is expressed by intestinal cells which is further associated with synthesis of cGMP and leads to cell cycle homeostasis mechanisms like cell proliferation, DNA repair, metabolic programming and epithelial-mesenchymal interactions organizing the epithelial crypt-surface axis [96–99]. GC-C is activated by paracrine hormones, uroguanylin (GUCA2B) and guanylin (GUCA2A). These ligands bind to GCC receptor and regulate various cellular processes. In colon cancer, these two hormones become lost which causes dysregulation in cell cycle and DNA repair mechanisms [100]. GCC is transmembrane receptor protein which is encoded by GUGY2C gene and is involved in intestinal cellular proliferation, regulation of electrolyte homeostasis, inflammation and mucosal function in the intestine [101–105]. Thus, dysregulation in GCC is involved with colon carcinogenesis. Other than colon cancer, its expression is also involved in gastrointestinal tumors [106] like adenocarcinoma of esophagus and stomach [107] and rectal cancers [108]. GUCY2C gene silencing leads to dysfunction in cell cycle and induces susceptibility for the development of colon cancer [98,109,110]. According to a study, GC-C gene silencing led to tumorigenesis in mice which suggests its involvement in the pathogenesis of colon cancer [111–114].

GC-C is used as a biomarker for colon cancer and it is now believed to be intestinal tumor suppressor receptor. *In vivo* $Apc^{min/+}$ and azoxymethane (AOM) induced colon cancer in mice showed a higher rate of tumor incidence with $GUCY2C^{-/-}$ than intact GUCY2C signaling [112]. Another *in vivo* study in $GUCY2C^{-/-}$ mice showed higher colonic cell proliferation and significantly decreased the amount of cGMP than $GUCY2C^{+/+}$ mice in MNU induced colon cancer [115]. Also, by the administration of 8-pCPT-cGMP attenuated aberrant crypt foci formation in wild type and $GUCY2C^{-/-}$ mice which suggests the beneficial role of cGMP in controlling colon cancer. Increase in cGMP also activated PKGII and MAPK signaling following which activation of p21 induced cell cycle arrest. These data suggest the role of GCC and cGMP are important in the treatment of colon cancer [115]. Further *in vivo* study proved that silencing of this gene is promoting the proliferation of cancer cells by activating oncogenes like cyclin D1, β-catenin, Rb gene, and pAKT and also downregulating tumor suppressor p27 and p21 genes [113–115]. MMP-9 is associated with colon cancer cell migration and invasion leading to metastatic tumors. Targeting MMP-9 is a novel approach for antimetastatic treatment [116,117]. In T84 and Caco-2 colon cancer cell lines, GCC and subsequent activation of cGMP reduce colon cancer tumor cell spreading and metastasis by regulation of tumor epithelial matrix metalloprotease (MMP-9) [118].

In a clinical study, GC-C has been detected in > 1000 samples of colon tissues and its expression at mRNA and protein levels were detected higher (> 80%) in colonic and rectal tissues [119–121]. GC-C RT-qPCR is useful in the detection of primary stage and metastatic colon cancer [122]. GC-C expression was analyzed by immunohistochemistry in gastrointestinal tumors including esophageal, gastric, pancreatic and colorectal primary and metastatic tumors of total 627 patients. From which it is consistently expressed in both primary and metastatic colorectal tumors which suggest the role of GCC throughout the process of tumorigenesis [106]. GC-C synthetic activator linaclotide is in the clinical pipeline for chemoprevention of colorectal cancer in healthy volunteers (clinicaltrials.gov NCT01950403). This trial demonstrated activation of GUCY2C leading to cGMP accumulation in intestinal epithelial cells. This activated vasodilator-stimulated phosphoprotein (VASP) and reduced Ki67-positive cells which suggest inhibition of proliferation [123]. Many preclinical and clinical data suggest an important beneficial role of GC activation and subsequent elevation of cGMP in colon cancer. Hence, these findings imply the key role of GC in treating colon cancer which can be further evaluated in clinical trials for their inhibitory effects on colon cancer.

4. Phosphodiesterase in colon cancer

PDEs are the enzymes that regulate the level of cAMP and cGMP through hydrolysis. PDE enzymes are encoded by 21 genes in humans [77] and classified in 11 different families (PDE1-PDE11) from which several of them contain isoform subfamilies. These PDEs differ in their 3D structure, cellular localization, cellular expression, kinetic properties and inhibitor sensitivity [77,124]. PDEs contain catalytic C domain

and regulatory N terminal domain. These domains mediate different signaling pathways and their regulation depends on cellular distribution and location with short term changes like phosphorylation, proteolysis and long-term changes at the transcriptional level [125,126]. Many tumors display a decreased level of intracellular cAMP as a consequence of high PDE expression [29]. First PDE inhibitor methylxanthine was found in 1962 [127] and non -selective PDE inhibitors papaverine and caffeine were getting used until potent PDE specific inhibitors came into the market [128,129]. Currently PDE inhibitors are being investigated for a variety of diseases like cognitive disorders [130], inflammatory airway disease [131] and inflammatory skin diseases [132], hypertension and renal vascular dysfunction [133] and various tumors [134].

PDE2 was previously known as cGMP-stimulated PDE which is regulated by cGMP. It is present in cardiac tissue and endothelial cells and hydrolyzes cAMP and cGMP with same V_{max} and K_m value [135]. Sulindac sulfone (exisulind) is an NSAIDS derivative which induces apoptosis in colon cancer cells independent of the cyclooxygenase pathway. It induces apoptosis *via* cGMP PDE2/5 inhibition [136,137]. Exisulind works through the inhibition of PDE2 and PDE5 isoforms [138]. In Familial Adenomatous Polyposis (FAP) patients with APC mutation, exisulind induces apoptosis and degradation of β-catenin which suggests induction of apoptosis through this wnt/β-catenin pathway [87,139,140]. This hypothesis was evaluated in colon cancer SW480 and HT29 cells from which SW480 cells are found to be the target of exisulind and its analogs in which it causes apoptosis following sustain release of cGMP, PDE2/5 inhibition, PKG activation and proteasomal degradation of β-catenin. Thus, these *in vitro* data are suggesting that PDE2 inhibitors may have a beneficial role in treating colon cancer as proapoptotic agents. However, further animal studies and clinical evaluations are necessary to confirm their role for anticancer effects in colon cancer.

PDE3 enzyme has two isoforms as PDE3A and PDE3B which are inhibited by cGMP in contrary to PDE2 enzyme. It has a high affinity towards both cAMP and cGMP but it hydrolyzes cAMP with ten times higher V_{max} than that of cGMP [51,141]. Both isoforms have different localization as PDE3A is localized in platelets and functions during thrombus formation while PDE3B is localized in peripheral blood T cells and fibroblasts [142–144]. On the other hand, both isoforms are localized in vascular smooth muscle and epithelial cells and facilitate inflammation through the NF-κB pathway [88].

PDE3 inhibitor cilastazol is used for the treatment of intermittent claudication in patients with peripheral artery disease. The mechanism involved is increase in cAMP level by inhibiting PDE3 [145,146]. Cilastazol is an anti-platelet agent and has been reported to exhibit beneficial effect in liver metastatic tumor owing to its inhibitory effect in the interaction of platelets and cancer cells [147,148]. This has been evaluated in human colon cancer cell line DLD-1 in which it attenuates colon cancer cell motility and inhibited cellular invasion by increasing level of cAMP [149]. These improvements are believed to be associated with an effect on cancer cells and platelets. Transcellular migration of tumor cells is also inhibited which has a beneficial effect for host cells. Cilastazol can be a novel anti-cancer drug which acts by inhibition of cancer cell invasion. Anti-proliferative properties are not evaluated yet but it might give beneficial results if given as a combination treatment with 5-FU or other anti-proliferative drugs like paclitaxel or cisplatin in the treatment of colon cancer [149].

Cyclic phosphatidic acid (cPA) is a bioactive lipid which elevates cAMP level by inhibition of PDE3B and has been reported to inhibit cancer cell proliferation and invasion. Colon cancer cell lines HT-29 and DLD-1 were used to find expression level of PDE3 isoforms, PDE3A and PDE3B. PDE3B levels are reported to affect colon cancer cell growth and their expression was found to be significantly higher in HT-29 cell lines but it was lower in DLD-1 cell lines. cPA treatment suppressed tumor cell growth in HT-29 by inhibiting PDE3B in a dose-dependent manner [150]. cPA treatment inhibited proliferation of HT-29 and LOVO cells expressing high levels of PDE3B but not in Caco-2 and DLD-1 cell lines which express a lower level of PDE3B. These findings suggest inhibition of PDE3B is associated with growth inhibition in colon cancer cells [150]. cPA treatment was also found to inhibit AKT phosphorylation in a dose-dependent manner and subsequent downstream processes involved with apoptosis and proliferation. Many tumors cells proliferation is found to be associated with AKT phosphorylation. AKT phosphorylation causes a decrease in the level of cAMP through activation of PDE3B and further leads to cell proliferation and suppression of apoptosis [151]. Thus, this leads to the conclusion that cPA treatment works though cPA-PDE3B-cAMP pathway and AKT dephosphorylation [150].

PDE4 is a large family of 35 isoforms subgroups with four genes (4A, 4B, 4C, 4D) and is selective for cAMP [152]. PDE4D is localized in inflammatory airways and smooth muscle cells while PDE4B is expressed higher in inflammatory cells. Thus, PDE4 inhibitors have been developed for the treatment of airway inflammatory disorders like COPD and asthma [18,153,154]. Other applications of PDE4 specific inhibitors are allergic rhinitis [155], depression [156] and psoriasis [157]. Higher expression of PDE4 is responsible for various cancer pathologies including colon cancer [158], melanoma [159], lymphoma [160,161], glioma [162], ovarian [163], brain tumors [164], non-small cell and small cell lung cancer [165]. Documented evidence suggests upregulation of PDE4B in oncogenic KRAS 3-dimensional colonic-crypt in HCT-116 cell lines [158]. Further, inhibition of PDE4 hydrolyzing activity produces luminal apoptosis in HCT116 colon cancer cell line [166,167]. Oncogenic KRAS mutation will disrupt the acinar structure and increase PDE4B expression leading to phosphorylation of AKT [158]. In public dataset analysis of 16 patients in which patients (n = 6) with relapsed CRC have acquired higher expression of PDE4B mRNA than that of the non-relapsed CRC patients (n = 10), suggesting poor prognosis and metastasis of CRC is associated with higher PDE4B expression [168]. This concludes the key role of PDE4 in development of cancer and as PDE4 inhibitors have been reported to have an anticancer role in many tumors, this class of agents can be a novel treatment approach for colon cancer as well.

Many *in vitro* and *in vivo* studies have reported the key role of PDE4 inhibitors in the treatment of various types of cancers. To find which PDEs are involved in colon cancer cell invasion and motility, PDE 2, 4 and 5 were used in colon cancer DLD-1 cells [169]. PDE4 specific inhibitors rolipram and Ro-20-1724 elevated cAMP level in DLD-1 cells but PDE2 inhibitors EHNA and PDE5 inhibitor zaprinast failed to do so [169]. Further, in chemotaxis assay, rolipram and Ro-20-1724 inhibited cancer cell motility in a dose-dependent manner but PDE2 and PDE5 inhibitors did not suppress motility. This concludes the key role of PDE4 enzyme in colon cancer cell motility which can further be evaluated as a novel target for colon cancer as an anti-invasion therapy [169]. Another study suggested in HCT116 cells that AKT phosphorylation was inhibited by rolipram and PDE4B3-shRNA producing beneficial effects [158].

Specific PDE4 inhibitor apremilast is approved for the treatment of inflammatory diseases like psoriasis and psoriatic arthritis [170,171] and it has lesser side effects compared to other PDE4 inhibitors like rolipram [172] in a colon cancer model with KRAS mutant gene and *in vitro* cell line, the effect of apremilast was studied. Apremilast significantly induced apoptosis in the 3D culture of HKe3-mtKRAS and HKe3-wtPDE4B2 cells through inhibition of PDE4B2 and caspase-1 activation [173].

Resveratrol is a natural plant derivative found in grapes and red wine and has got similar inhibitory action on PDE4 as of rolipram [174]. Many *in vitro* and *in vivo* studies have been reported to have its role in colon cancer. Resveratrol produces the formation of luminal cavity and apoptosis of multicellular spheroidal HCT116 cells. It directly inhibits PDE4 activity and hence increasing cAMP leading to the formation of luminal cavity and apoptosis. These results were similar to the selective PDE4 inhibitor rolipram. Because of lower toxicity and

efficacy of resveratrol, it may be useful as a chemopreventive therapy in colon cancer [167]. Another study was carried out in LoVo cell lines which have shown anti-proliferative and apoptotic effects of resveratrol which was due to upregulation of bone morphogenetic protein 9 (BMP9) expression [175]. Increased expression of BMP9 was also contributed to the activation of p38 MAPK. These results were also confirmed *in vivo* xenograft model in athymic mice. Resveratrol effectively inhibited the growth of tumor *in vivo* model. From this study, we can conclude that resveratrol partly works through BMP9 and p38 MAPK pathway for its anticancer effects [175]. Inhibition of cell proliferation is reported by many authors *in vitro* cell line studies including HT-29 [176–179], Caco-2 [180–182], HCT-115 [181], SW480 [183] and RKO [177]. It also has a role in the induction of apoptosis in colon cancer inhibition. Many studies showing resveratrol and its effects on the apoptotic pathway leading to tumor cell death. In HT-29 cell line, it induces ROS production leading to the cytochrome-c release and subsequent activation of procaspase-9 and downstream apoptotic molecules [184]. Also, apoptosis in HT-29 cells by resveratrol was carried out by activation of lysosomal cathepsin followed by caspase activation in the endoplasmic reticulum [185]. This increases the expression of apoptotic genes CHOP/GADD153 [186]. In SW480, SW620 and HT-29 cell lines, trans-resveratrol is reported to have apoptotic action *via* activation of the MAPK pathway and its accumulation in lipid-raft [187]. It also causes monensin induced active endocytosis. These two events are owing to the activation of the caspase pathway in colon cancer cell lines [187]. HCT-116 cell line study showed to inhibit PI3K/Akt signaling and an increase in PTEN expression leading to anti-proliferative actions of resveratrol. m-RNA expression of β-catenin was also decreased in a dose-dependent manner. This study was also carried out in xenograft athymic mice model which showed similar results to *in vitro* study. Hence, these results suggest that resveratrol inhibits proliferation of colon cancer cells *via* PTEN/PI3K/Akt and Wnt/β-catenin pathway [188].

In vivo efficacy of resveratrol was also prominent and has been reported by many authors in different animal models. In 1,2-dimethyl hydrazine (DMH) induced rat model, resveratrol and its metabolites inhibited ACF by 58% and 48% in medial and distal colon respectively [189]. Active metabolites of resveratrol showing anticancer effects are dihydroresveratrol, trans-resveratrol glucuronide and its sulfate conjugates [189,190]. In OM induced colon cancer in F344 rats, resveratrol inhibited proliferation and induced apoptosis *via* modulation Bax and p21 expression [191]. DMH induced COX-2 elevation was also reverted by the administration of resveratrol which is associated with apoptosis, anti-angiogenesis and immunomodulatory role in colon cancer [192]. It also induced expression of heat shock protein 80 and caspase 3 in DMH induced rat model [192]. Several studies have mentioned the role of anti-oxidant modulating effects of resveratrol in DMH/AOM induced colon cancer. Resveratrol increased the activity of glutathione reductase, superoxide dismutase, catalase, and reduced glutathione while diminishing activity of over-expressed glutathione peroxidase and glutathione S-transferase [193]. In genetically modified Apc^{min} mice, resveratrol completely suppressed tumors in the colon with also decreased number of tumors in the small intestine [194]. However, another author has reported contradictory results of resveratrol in $Apc^{min/+}$ mice in which resveratrol does not show any effect in intestinal tumorigenesis [195]. In concluding, these studies are showing a major anticancer role of resveratrol which can be used as a novel treatment for colon cancer patients with further clinical evaluation.

Chemoresistance is a major problem associated with the treatment of colon cancer [196]. Colon cancer resistance cells KM12C are found to be resistant to cytotoxic agents acting through DNA damage and other commonly used cytotoxic drugs [66]. Their growth is dependent on PI3K/AKT signaling pathway and PTEN expression which negatively regulates the PI3K/AKT pathway [197,198]. Low dose of forskolin (AC activator) and rolipram (PDE4 inhibitor) but not PDE3 inhibitor cilostamide, inhibited KM12C growth by overcoming resistance and deactivation of phosphoinositol-3, 4, 5-triphosphate/PI3K signaling [66]. This leads to inhibition of AKT/PKB pathway. In addition, expression of PTEN which is lost in cancer cells was sensitized with a low dose of forskolin. Combination of a low dose of forskolin (1 μM/L) and rolipram (10 μM/L) have shown complete growth inhibition than a low dose of forskolin alone which produced only 50% growth inhibition. Rolipram alone did not show any effect on growth inhibition in KM12C cells. Moreover, the expression of $p21^{KIP1}$ was increased which leads to a decrease in the expression level of associated cyclins A, B_1, and E and CDK by high dose forskolin and a combination of low dose forskolin and rolipram. This induces cell cycle arrest at the G_1-S phase *via* the pRB/cyclin/CDK pathway. It also inhibited cell viability by increasing cAMP levels through activation of AC in KM12C cells. The further evaluation suggested that out of 11 other cell lines, three of them KM12C, MCF7 and HT29 are found to be sensitive with this treatment at 80% of growth inhibition. Other five cell lines A431, WiDr, RKO, A375, and H630 has shown 40–60% inhibition of growth while remaining three cell lines Dul45, SW480 and SW620 were insensitive to forskolin/rolipram treatment. This concluded sensitivity of KM12C cells is associated with cAMP elevation by PDE4 inhibition, AC activation, and inhibition of the PI3K signaling pathway [66]. PDE4 inhibitors have shown a wide range of anticancer effects through inhibition of colon cancer cell growth, proliferation, invasion and angiogenesis in both *in vivo* and *in vitro* models. Moreover, PDE4 inhibitor resveratrol is being evaluated in a clinical trial for its anticancer effects in colon cancer. Since clinically PDE4 has shown to have high expression in colon cancer cells it can be used as a novel target for colon cancer treatment.

PDE5 is encoded with PDE5A gene with three isoforms PDE5A1, PDE5A2 and PDE5A3. PDE5 catalyzes cGMP and expressed mainly in smooth muscle cells of corpus cavernosum and also in other vascular smooth muscles, skeletal muscles, immune cells, and platelets [199]. Studies reported its higher expression levels in different malignancies like non-small cell lung cancer [24–26], urinary bladder cancer [27,28] and metastatic breast cancer [200]. Expression of PDE5 is higher in colon adenomas and adenocarcinomas compared to the normal colonic mucosa. None from normal colonic mucosa showed positive labeling of PDE5 but 5 of 5 adenomas and 11 of 13 adenocarcinomas showed positive labeling. This evidence suggested increased expression of PDE5 in colon cancer cells [201]. PDE5 inhibitors sildenafil, vardenafil, and tadalafil are generally indicated in the treatment of erectile dysfunction. *In vivo*1, 2-dimethyl hydrazine induced colon cancer rat model was used to evaluate the effect of sildenafil and pentoxifylline in combination to first-line therapy 5-FU. In DMH induced model, the expression level of tumor markers carcinoembryonic antigen (CEA), carbohydrate 19-9 (CA19-9) antigen and caspase-3 a marker for apoptosis were determined. Plasma level of CEA and CA19-9 decreased in rats treated with 5-FU plus pentoxifylline and sildenafil plus pentoxifylline treatment while caspase-3 levels got increased with 5-FU plus sildenafil and 5-FU plus pentoxifylline. cGMP works by downstream activation of PKG which leads to apoptosis and growth inhibition of cancer cells. In many cancers, PKG is downregulated. PDE5 inhibitors work through an increase in cGMP and subsequent apoptosis pathway in colon cancer cells [89].

As previously stated, exisulind (an NSAID) works by inhibition of PDE enzyme to produce anti-proliferative effects in colon cancer cells [138]. Series of NSAID derivatives have shown to inhibit colon cancer growth by increasing cGMP level with no correlation to the cyclooxygenase pathway [201]. HT-29 treated with non-COX inhibitor sulindac sulfone and sulfoxide derivative were compared with highly specific COX-2 antagonist rofecoxib and COX-1 antagonist indomethacin. Despite COX inhibitory effects, sulindac derivatives inhibited the growth of HT29 cells by inhibition of cGMP PDE. Indomethacin has also shown inhibitory effects on cGMP specific PDE5 but with lower efficacy compared to sulindac sulfone despite its higher potency for COX-1 and COX-2. All other NSAIDs showed lesser effects in reduction of HT29 growth. These data suggested that growth of colon cancer cells is

Table 2
Clinical trials of PDE inhibitors in colon cancer.

Treatment	Trial phase	Key results	Status	Reference
Atorvastatin calcium, oligofructose-enriched insulin, or sulindac	Phase II	The trial did not provide convincing evidence for reduction of CRC risk from 6 months of treatments.	Completed	https://clinicaltrials.gov/ct2/show/NCT00335504
Comparison of sulindac, aspirin, and ursodiol	Phase II	Study closed by NCI.	Terminated	https://clinicaltrials.gov/ct2/show/NCT00062023
Dietary polyamines-difluoromethylornithine (DFMO) and sulindac	Phase III	Significant metachronous adenoma risk reduction was found in DMFO + sulindac groups with lower and median dose of dietary polyamines but not in highest dose.	Completed	Raj et al. [204]
Eflornithine and sulindac	Phase III		Completed	https://clinicaltrials.gov/ct2/show/NCT00118365
Eflornithine plus sulindac	Phase III	–	Recruiting	https://clinicaltrials.gov/ct2/show/NCT01349881
Eflornithine plus sulindac	Phase III	–	Active, not recruiting	https://clinicaltrials.gov/ct2/show/NCT01483144
Exisulind	Phase II	Principle Investigator has left the University.	Withdrawn	https://clinicaltrials.gov/ct2/show/NCT00026468
Nivolumab (anti-PD1), tadalafil and oral vancomycin	Phase II	–	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT03785210
Resveratrol	Phase I	Resveratrol inhibits Wnt pathway in normal colonic mucosa but not in colon cancer patients.	Completed	Nguyen et al. [205] https://clinicaltrials.gov/ct2/show/NCT00256334
Resveratrol	Phase I	Results not posted	Completed	https://clinicaltrials.gov/ct2/show/NCT00433576
Sulindac	Not applicable	Study completed.	Terminated	https://clinicaltrials.gov/ct2/show/NCT00003365
Sulindac and erlotinib	Phase II	Combination of sulindac and erlotinib resulted in lower burden of duodenal polyps after 6 months with grade 1 and 2 adverse events in 87% patients.	Completed	Samadder et al. [206] https://clinicaltrials.gov/ct2/show/NCT01187901
Surgery plus sulindac or surgery alone	Phase II	The trial was prematurely closed due to lack of accrual.	Terminated	https://clinicaltrials.gov/ct2/show/NCT01856322
Udenafil	Phase II	Results not posted	Completed	https://clinicaltrials.gov/ct2/show/NCT00607282x

sensitive to PDE inhibition and not related to cyclooxygenase inhibition. Adenylate cyclase activator forskolin failed to reduce growth in HT29, HCT116 and SW480 cell lines suggesting cGMP PDE inhibition is responsible for anti-proliferative action in these cell lines. *In vivo* efficacy of sulindac was assessed in HT29 colon cancer xenograft mouse model which decreased 55% growth of tumor than the vehicle control group. The study concluded that cGMP PDE pathway and inhibition of β-catenin transcription through NSAIDs derivatives can be used as a novel target to treat colon cancer [201].

In vitro evaluation of chemically modified sulindac and ADT-094 as a form of a dual inhibitor of PDE5 and PDE10 inhibited tumor growth of HCT116 cells by cGMP/PKG signaling and suppression of β-catenin, T-cell factor (TCF) transcription, cyclin D1, and survivin. This suggested dual inhibition as a novel approach for the treatment of colon cancer [90]. Chronic inflammatory conditions like IBD and colitis may lead to carcinogenesis of the colon [202]. In an inflammation derived colon cancer mouse model, sildenafil reduced polyp multiplicity by 50% than normal disease control mice model. DSS induced colitis and subsequent azoxymethane/dextran sulfate sodium (AOM/DSS) induced colon cancer in mice was treated with sildenafil. Sildenafil protected the intestinal epithelium from DSS injury and suppressed polyp formation in AOM/DSS colon cancer model through activation of cGMP signaling and phosphorylation of PKG substrate vasodilator-stimulated phosphoprotein (VASP) [91]. Polyps treated with sildenafil were less inflamed which is acting through iNOS and INFγ pathway. Early carcinogenesis was prevented by sildenafil with 50% reduction in polyp multiplicity. Also, in a later stage of cancer development, sildenafil treatment showed similar results through an increase in mucus formation, a decrease in the level of pro-inflammatory cytokines and anti-proliferative action. However, sildenafil did not show any apoptotic effects in polyps, although they were less proliferative in sildenafil treated colon cancer group [91]. As like PDE4 inhibitors, these class of agents also have a wide range of anticancer properties in both *in vitro* and *in vivo* colon cancer models as well as in clinical trials. Further research can be done to evaluate the beneficial role of PDE5 inhibitors for colon cancer patients.

PDE10 is cGMP specific enzyme which has limited distribution including in brain and testes. It plays a key role in cognition [203]. PDE10 expressions are increased in colon cancer adenocarcinoma cell lines HT29, HCT116, Caco-2 and SW-48 than normal colonocytes. In human colon cancer cells among 40 colon cancer patients, 29 showed an increased level of PDE10 mRNA compared with 8 normal colonocytes [92]. Selective PDE10 inhibitors papaverine, PQ-10, and Pf-2545920 suppressed growth in human cancer cell lines HT29, SW480 and HCT116. Pf-2545920 increased caspase-3 and -7 to induce apoptosis and inhibited DNA synthesis in a dose-dependent manner in HT29 cancer cell lines. Further siRNA knockdown of PDE10 inhibited colon tumor growth. It has also inhibitory effects on cGMP hydrolysis and PKG activation which leads to suppression of Wnt/β-catenin signaling and TCF transcriptional activity in HCT116 and HT29 cells. As in contrast over expressing PDE10 cell lines, exhibited increased growth of tumors by activation of β-catenin, cyclin D1, and survivin. *In vivo*, $Apc^{Min/+}$ mouse model showed a higher level of PDE10 mRNA compared to normal mucosa from wild type Apc mice. These all data suggested PDE10 had higher expression in colon cancer that can be used as a novel target to inhibit colon cancer through cGMP PKG and wnt/β-catenin signaling pathway [92]. *In vivo* study showing higher expression of PDE10 in colon cancer cells and anticancer role of PDE10 inhibitors in different *in vitro* models are pointing towards the fact that it can be used as a novel target with further evaluation in animal models and clinical research.

5. Conclusion

Colon cancer is one of the fastest growing cancers and five-year survival rate is lower in developing countries due to limited resources and inadequate health infrastructure. Despite newer screening technologies, > 25% of the patients are diagnosed with metastatic cancer. Major obstacles to colon cancer treatment are relapses after surgical resection and resistant to existing chemotherapeutic agents. Resistant to adjuvant therapies like 5-FU, capecitabine and other first-line therapies are developed within 3–12 months of the treatment. This is why novel targets are needed for the treatment of resistant colon cancer. With the development of newer diagnostic techniques, PDE enzymes have been reported to have increased expression in colon cancer patients. Higher expression of PDE in colon cancer patients leads to poor prognosis and tumor metastasis. PDEs hydrolyze cyclic nucleotides (cAMP and cGMP) and causes tumorigenic effects in the colon. Inhibition of these enzymes could result in beneficial effects in treating colon cancer. Many *in vitro* and *in vivo* studies have confirmed inhibition of PDEs leads to tumor cell apoptosis, inhibition of tumor cell proliferation, inhibition of angiogenesis and tumor cell invasion and motility. Several PDE inhibitors like resveratrol, tadalafil, sildenafil, udenafil, and sulindac are currently in the clinical trial pipeline for the treatment of colon cancer (Table 2). With the help of novel techniques including western blot analysis and gene expression studies, we can further identify downstream signaling molecules and pathways which lead to anticancer effects of PDE inhibitors. With this, we can conclude that PDE inhibitors can be used as monotherapy or in combination with other chemotherapeutic agents to have beneficial effects and overcome resistance in colon cancer patients.

Declaration of Competing Interest

None.

References

[1] American Cancer Society, https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html , Accessed date: 12 March 2018.
[2] National Cancer Institute, https://seer.cancer.gov/statfacts/html/colorect.html , Accessed date: 12 March 2018.
[3] D. Sharma, G. Singh, Clinico-pathological profile of colorectal cancer in first two decades of life: a retrospective analysis from tertiary health center, Indian J. Cancer 54 (2) (2017) 397.
[4] F. Amersi, M. Agustin, C.Y. Ko, Colorectal cancer: epidemiology, risk factors, and health services, Clinics in colon and rectal surgery 18 (03) (2005) 133–140.
[5] C.M. Johnson, C. Wei, J.E. Ensor, D.J. Smolenski, C.I. Amos, B. Levin, D.A. Berry, Meta-analyses of colorectal cancer risk factors, Cancer Causes Control 24 (6) (2013) 1207–1222.
[6] C.E. Desch, A.B. Benson 3rd, M.R. Somerfield, P.J. Flynn, C. Krause, C.L. Loprinzi, N.J. Petrelli, Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline, J. Clin. Oncol. 23 (33) (2005) 8512–8519.
[7] F. Guyot, J. Faivre, S. Manfredi, B. Meny, C. Bonithon-Kopp, A.M. Bouvier, Time trends in the treatment and survival of recurrences from colorectal cancer, Ann. Oncol. 16 (5) (2005) 756–761.
[8] A.G. Renehan, M. Egger, M.P. Saunders, S. T O'Dwyer, Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials, Bmj 324 (7341) (2002) 813.
[9] D.P. Ryan, Novel therapies in colon cancer, Current Colorectal Cancer Reports 2 (3) (2006) 116–119.
[10] D. Cunningham, Y. Humblet, S. Siena, D. Khayat, H. Bleiberg, A. Santoro, I. Chau, Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer, N. Engl. J. Med. 351 (4) (2004) 337–345.
[11] E. Van Cutsem, M. Peeters, S. Siena, Y. Humblet, A. Hendlisz, B. Neyns, M. Wolf, Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer, J. Clin. Oncol. 25 (13) (2007) 1658–1664.
[12] E.W. Sutherland, T.W. Rall, Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles, J. Biol. Chem. 232 (2) (1958) 1077–1092.
[13] D.A. Wallace, L.A. Johnston, E. Huston, D. MacMaster, T.M. Houslay, Y.F. Cheung, R.G. Knowles, Identification and characterization of PDE4A11, a novel, widely expressed long isoform encoded by the human PDE4A cAMP phosphodiesterase gene, Mol. Pharmacol. 67 (6) (2005) 1920–1934.
[14] M. Packer, J.R. Carver, R.J. Rodeheffer, R.J. Ivanhoe, R. DiBianco, S.M. Zeldis, G.I. Mallis, Effect of oral milrinone on mortality in severe chronic heart failure, N. Engl. J. Med. 325 (21) (1991) 1468–1475.
[15] W.M. Brown, Cilomilast GlaxoSmithKline, Curr. Opin. Investig. Drugs 6 (5) (2005) 545–558.
[16] K.F. Rabe, E.D. Bateman, D. O'Donnell, S. Witte, D. Bredenbröker, T.D. Bethke, Roflumilast—an oral anti-inflammatory treatment for chronic obstructive

pulmonary disease: a randomised controlled trial, Lancet 366 (9485) (2005) 563–571.
[17] A.I.F. Scott, A.F. Perini, P.A. Shering, L.J. Whalley, In-patient major depression: is rolipram as effective as amitriptyline, Eur. J. Clin. Pharmacol. 40 (2) (1991) 127–129.
[18] T.J. Torphy, B.J. Undem, Phosphodiesterase inhibitors: new opportunities for the treatment of asthma, Thorax 46 (7) (1991) 512.
[19] L.J. Ignarro, P.A. Bush, G.M. Buga, K.S. Wood, J.M. Fukuto, J. Rajfer, Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle, Biochem. Biophys. Res. Commun. 170 (2) (1990) 843–850.
[20] R.M. Rudd, A.R. Gellert, P.R. Studdy, D.M. Geddes, Inhibition of exercise-induced asthma by an orally absorbed mast cell stabilizer (M & B 22,948), British journal of diseases of the chest 77 (1983) 78–86.
[21] F.R. Faucz, A. Horvath, A. Rothenbuhler, M.Q. Almeida, R. Libe, M.L. Raffin-Sanson, J. Bertherat, D.M. Carraro, F.A. Soares, G. de Campos Molina, A.H. Campos, Phosphodiesterase 11A (PDE11A) genetic variants may increase susceptibility to prostatic cancer, The Journal of Clinical Endocrinology & Metabolism 96 (1) (2011) E135–E140 Jan 1.
[22] A. Horvath, L. Korde, M.H. Greene, R. Libe, P. Osorio, F.R. Faucz, M.L. Raffin-Sanson, K.M. Tsang, L. Drori-Herishanu, Y. Patronas, E.F. Remmers, Functional phosphodiesterase 11A mutations may modify the risk of familial and bilateral testicular germ cell tumors, Cancer Res. 69 (13) (2009) 5301–5306 Jul 1.
[23] D.D. Zhang, Y. Li, Y. Xu, J. Kim, S. Huang, Phosphodiesterase 7B/microRNA-200c relationship regulates triple-negative breast cancer cell growth, Oncogene 38 (7) (2019) 1106 Feb.
[24] C.M. Whitehead, K.A. Earle, J. Fetter, S. Xu, T. Hartman, D.C. Chan, T.L. Zhao, G. Piazza, A.J. Klein-Szanto, R. Pamukcu, H. Alila, Exisulind-induced apoptosis in a non-small cell lung cancer orthotopic lung tumor model augments docetaxel treatment and contributes to increased survival, Mol. Cancer Ther. 2 (5) (2003 My 1) 479–488.
[25] C.M. Whitehead, K.A. Earle, J. Fetter, S. Xu, T. Hartman, D.C. Chan, T.L. Zhao, G. Piazza, A.J. Klein-Szanto, R. Pamukcu, H. Alila, Exisulind-induced apoptosis in a non-small cell lung cancer orthotopic lung tumor model augments docetaxel treatment and contributes to increased survival, Mol. Cancer Ther. 2 (5) (2003 May 1) 479–488.
[26] C.M. Whitehead, K.A. Earle, J. Fetter, S. Xu, T. Hartman, D.C. Chan, ... H. Alila, Exisulind-induced apoptosis in a non-small cell lung cancer orthotopic lung tumor model augments docetaxel treatment and contributes to increased survival, Mol. Cancer Ther. 2 (5) (2003) 479–488.
[27] G.A. Piazza, W.J. Thompson, R. Pamukcu, H.W. Alila, C.M. Whitehead, L. Liu, J.R. Fetter, W.E. Gresh, A.J. Klein-Szanto, D.R. Farnell, I. Eto, Exisulind, a novel proapoptotic drug, inhibits rat urinary bladder tumorigenesis, Cancer Res. 61 (10) (2001) 3961–3968 May 15.
[28] G.A. Piazza, W.J. Thompson, R. Pamukcu, H.W. Alila, C.M. Whitehead, L. Liu, ... I. Eto, Exisulind, a novel proapoptotic drug, inhibits rat urinary bladder tumorigenesis, Cancer Res. 61 (10) (2001) 3961–3968.
[29] L. Hirsh, A. Dantes, B.S. Suh, Y. Yoshida, K. Hosokawa, K. Tajima, A. Amsterdam, Phosphodiesterase inhibitors as anti-cancer drugs, Biochem. Pharmacol. 68 (6) (2004) 981–988.
[30] G.L. Powers, K.D. Hammer, M. Domenech, K. Frantskevich, R.L. Malinowski, W. Bushman, D.J. Beebe, P.C. Marker, Phosphodiesterase 4D inhibitors limit prostate cancer growth potential, Mol. Cancer Res. 13 (1) (2015) 149–160 Jan 1.
[31] D.U. Kim, B. Kwak, S.W. Kim, Phosphodiesterase 4B is an effective therapeutic target in colorectal cancer, Biochem. Biophys. Res. Commun. 508 (3) (2019) 825–831 Jan 15.
[32] H.Y. Zhao, Y.H. Ren, X.B. Ren, Y. Wang, Diprophylline inhibits non-small cell lung cancer A549 cell proliferation and migration, and promotes apoptosis, by down-regulating PI3K signaling pathway, Oncol. Lett. 17 (1) (2019) 857–862 Jan 1.
[33] P. Vandenberghe, M. Delvaux, P. Hagué, C. Erneux, J.M. Vanderwinden, Potentiation of imatinib by cilostazol in sensitive and resistant gastrointestinal stromal tumor cell lines involves YAP inhibition, Oncotarget 10 (19) (2019) 1798 Mar 5.
[34] T. Peng, J. Gong, Y. Jin, Y. Zhou, R. Tong, X. Wei, L. Bai, J. Shi, Inhibitors of phosphodiesterase as cancer therapeutics, Eur. J. Med. Chem. 150 (2018) 742–756. Apr 25.
[35] P. Lv, W. Wang, Z. Cao, D. Zhao, G. Zhao, D. Li, L. Qi, J. Xu, Fsk and IBMX inhibit proliferation and proapoptotic of glioma stem cells via activation of cAMP signaling pathway, J. Cell. Biochem. 120 (1) (2019) 321–331 Jan.
[36] A. Richard, H.M. Abdel-Rahman, J.H. Kim, L. Vukadin, G.A. Piazza, E.Y. Ahn, A Novel Quinazolin-4 (3H)-one/Schiff Base Hybrid Phosphodiesterase 4 Inhibitor as a Potential Therapeutic Agent for Leukemia, (2018), p. 891.
[37] V. Lavoué, P. Legembre, J. Levêque, F. Foucher, S. Henno, F. Cabillic, Ovarian cancer immunity. Ovarian Cancer Immunotherapy. (2018) 34. Aug 31.
[38] A. Fajardo, G. Piazza, H. Tinsley, The role of cyclic nucleotide signaling pathways in cancer: targets for prevention and treatment, Cancers 6 (1) (2014) 436–458.
[39] N. Gerits, S. Kostenko, A. Shiryaev, M. Johannessen, U. Moens, Relations between the mitogen-activated protein kinase and the cAMP-dependent protein kinase pathways: comradeship and hostility, Cellular signaling 20 (9) (2008) 1592–1607.
[40] P. Sassone-Corsi, The cyclic AMP pathway, Cold Spring Harb. Perspect. Biol. 4 (12) (2012) a011148.
[41] J. Hanoune, N. Defer, Regulation and role of adenylyl cyclase isoforms, Annu. Rev. Pharmacol. Toxicol. 41 (1) (2001) 145–174.
[42] L.C. Lee, D.H. Maurice, G.S. Baillie, Targeting protein–protein interactions within the cyclic AMP signaling system as a therapeutic strategy for cardiovascular disease, Future Med. Chem. 5 (4) (2013) 451–464.
[43] A. Robinson-White, C.A. Stratakis, Protein kinase A signaling: “cross-talk” with other pathways in endocrine cells, Ann. N. Y. Acad. Sci. 968 (1) (2002) 256–270.
[44] A. Robinson-White, T.R. Hundley, M. Shiferaw, J. Bertherat, F. Sandrini, C.A. Stratakis, Protein kinase-A activity in PRKAR1A-mutant cells, and regulation of mitogen-activated protein kinases ERK1/2, Hum. Mol. Genet. 12 (13) (2003) 1475–1484.
[45] A.J. Robinson-White, W.W. Leitner, E. Aleem, P. Kaldis, I. Bossis, C.A. Stratakis, PRKAR1A inactivation leads to increased proliferation and decreased apoptosis in human B lymphocytes, Cancer Res. 66 (21) (2006) 10603–10612.
[46] J.D. Scott, Cyclic nucleotide-dependent protein kinases, Pharmacol. Ther. 50 (1) (1991) 123–145.
[47] Y.H. Ahn, J.M. Jung, S.H. Hong, 8-Chloro-cyclic AMP–induced growth inhibition and apoptosis is mediated by p38 mitogen-activated protein kinase activation in HL60 cells, Cancer Res. 65 (11) (2005) 4896–4901.
[48] Y.S. Cho-Chung, T. Clair, J.S. Bodwin, B. Berghoffer, Growth arrest and morphological change of human breast cancer cells by dibutyryl cyclic AMP and L-arginine, Science 214 (4516) (1981) 77–79.
[49] D. Katsaros, G. Tortora, P. Tagliaferri, T. Clair, S. Ally, L. Neckers, Y.S. Cho-Chung, Site-selective cyclic AMP analogs provide a new approach in the control of cancer cell growth, FEBS Lett. 223 (1) (1987) 97–103.
[50] S.N. Kim, Y.H. Ahn, S.G. Kim, S.D. Park, Y.S. Cho-Chung, S.H. Hong, 8-Cl-cAMP induces cell cycle-specific apoptosis in human cancer cells, Int. J. Cancer 93 (1) (2001) 33–41.
[51] C. Lugnier, Cyclic nucleotide phosphodiesterase (PDE) superfamily: a new target for the development of specific therapeutic agents, Pharmacol. Ther. 109 (3) (2006) 366–398.
[52] G. Tortora, F. Ciardiello, Protein kinase A as target for novel integrated strategies of cancer therapy, Ann. N. Y. Acad. Sci. 968 (1) (2002) 139–147.
[53] J.L. Bos, Epac proteins: multi-purpose cAMP targets, Trends Biochem. Sci. 31 (12) (2006) 680–686.
[54] Y.S. Cho-Chung, T. Clair, P. Tagliaferri, S. Ally, D. Katsaros, G. Tortora, R.K. Robins, Site-selective cyclic AMP analogs as new biological tools in growth control, differentiation, and proto-oncogene regulation, Cancer Investig. 7 (2) (1989) 161–177.
[55] C.C. Carlson, L.L. Burnham, R.A. Shanks, D.T. Dransfield, 8-Cl-adenosine induces differentiation in LS174T cells, Dig. Dis. Sci. 46 (4) (2001) 757–764.
[56] H.M. Wang, N.G. Zheng, J.L. Wu, C.C. Gong, Y.L. Wang, Dual effects of 8-Br-cAMP on differentiation and apoptosis of human esophageal cancer cell line Eca-109, World J Gastroenterol: WJG 11 (41) (2005) 6538.
[57] C. Bianco, G. Tortora, G. Baldassarre, R. Caputo, G. Fontanini, S. Chine, F. Ciardiello, 8-Chloro-cyclic AMP inhibits autocrine and angiogenic growth factor production in human colorectal and breast cancer, Clin. Cancer Res. 3 (3) (1997) 439–448.
[58] C. Rohlff, T. Clair, Y.S. Cho-Chung, 8-Cl-cAMP induces truncation and down-regulation of the RI alpha subunit and up-regulation of the RII beta subunit of cAMP-dependent protein kinase leading to type II holoenzyme-dependent growth inhibition and differentiation of HL-60 leukemia cells, J. Biol. Chem. 268 (8) (1993) 5774–5782.
[59] B.D. Valle-Pérez, O.M. Martínez-Estrada, S. Vilaró, F. Ventura, F. Viñals, cAMP inhibits TGFβ1-induced in vitro angiogenesis, FEBS Lett. 569 (1–3) (2004) 105–111.
[60] H. Yokozaki, G. Tortora, S. Pepe, E. Maronde, H.G. Genieser, B. Jastorff, Y.S. Cho-Chung, Unhydrolyzable analogues of adenosine 3′: 5′-monophosphate demonstrating growth inhibition and differentiation in human cancer cells, Cancer Res. 52 (9) (1992) 2504–2508.
[61] M.V. Saba, D.H. Barkla, P.J. Tutton, Influence of adenosine cyclic nucleotide analogs on growth of human colon tumor cell lines, Life Sci. 47 (4) (1990) 307–311.
[62] R.M. Niles, K.W. Ludwig, J.S. Makarski, Differential growth inhibition in two human carcinoma cell lines by cyclic adenosine 5′-monophosphate analogs, J. Natl. Cancer Inst. 63 (4) (1979) 909–911.
[63] M.L. Steer, Adenyl cyclase, Ann. Surg. 182 (5) (1975) 603.
[64] M.G. Ludwig, K. Seuwen, Characterization of the human adenylyl cyclase gene family: cDNA, gene structure, and tissue distribution of the nine isoforms, Journal of Receptors and Signal Transduction 22 (1–4) (2002) 79–110.
[65] P.E. Graves, E.A. Surwit, J.R. Davis, R.L. Stouffer, Adenylate cyclase in human ovarian cancers: sensitivity to gonadotropins and nonhormonal activators, Am. J. Obstet. Gynecol. 153 (8) (1985) 877–882.
[66] D.G. McEwan, V.G. Brunton, G.S. Baillie, N.R. Leslie, M.D. Houslay, M.C. Frame, Chemoresistant KM12C colon cancer cells are addicted to low cyclic AMP levels in a phosphodiesterase 4–regulated compartment via effects on phosphoinositide 3-kinase, Cancer Res. 67 (11) (2007) 5248–5257.
[67] R.L. Nelson, O. Holian, Adenylate cyclase activity and cyclic adenosine monophosphate levels in colon cancer lines and dermal fibroblasts and the effects of cholera toxin and epidermal growth factor, J. Surg. Oncol. 38 (2) (1988) 108–112.
[68] M. Piontek, K.J. Hengels, R. Porschen, G. Strohmeyer, Protein kinase C and adenylate cyclase as targets for growth inhibition of human gastric cancer cells, J. Cancer Res. Clin. Oncol. 119 (12) (1993) 697–699.
[69] A. Appukuttan, J.P. Flacke, H. Flacke, A. Posadowsky, H.P. Reusch, Y. Ladilov, Inhibition of soluble adenylyl cyclase increases the radiosensitivity of prostate cancer cells, Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1842 (12) (2014) 2656–2663.
[70] A.M. El-Mowafy, M. Alkhalaf, Resveratrol activates adenylyl-cyclase in human breast cancer cells: a novel, estrogen receptor-independent cytostatic mechanism, Carcinogenesis 24 (5) (2003) 869–873.
[71] L. Gamet, J.C. Murat, A. Remaury, C. Remesy, P. Valet, H. Paris, C. Denis-Pouxviel,

Vasoactive intestinal peptide and forskolin regulate proliferation of the HT29 human colon adenocarcinoma cell line, J. Cell. Physiol. 150 (3) (1992) 501–509.
[72] H. Yi, K. Wang, J.F. Jin, H. Jin, L. Yang, Y. Zou, ... X. Liu, Elevated adenylyl cyclase 9 expression is a potential prognostic biomarker for patients with colon cancer, Medical science monitor: international medical journal of experimental and clinical research 24 (2018) 19.
[73] J.P. Flacke, H. Flacke, A. Appukuttan, R.J. Palisaar, J. Noldus, B.D. Robinson, Y. Ladilov, Type 10 soluble adenylyl cyclase is overexpressed in prostate carcinoma and controls proliferation of prostate cancer cells, J. Biol. Chem. 288 (5) (2013) 3126–3135.
[74] H. Kimura, F. Murad, Evidence for two different forms of guanylate cyclase in rat heart, J. Biol. Chem. 249 (21) (1974) 6910–6916.
[75] B.J. Wedel, D.C. Foster, D.E. Miller, D.L. Garbers, A mutation of the atrial natriuretic peptide (guanylyl cyclase-A) receptor results in a constitutively hyperactive enzyme, Proc. Natl. Acad. Sci. 94 (2) (1997) 459–462.
[76] H. Rehmann, A. Wittinghofer, J.L. Bos, Capturing cyclic nucleotides in action: snapshots from crystallographic studies, Nat. Rev. Mol. Cell Biol. 8 (1) (2007) 63.
[77] K. Omori, J. Kotera, Overview of PDEs and their regulation, Circ. Res. 100 (3) (2007) 309–327.
[78] D.F. Ashman, R. Lipton, M.M. Melicow, T.D. Price, Isolation of adenosine 3′, 5′-monophosphate and guanosine 3′, 5′-monophosphate from rat urine, Biochem. Biophys. Res. Commun. 11 (4) (1963) 330–334.
[79] F. Fallahian, F. Karami-Tehrani, S. Salami, M. Aghaei, Cyclic GMP induced apoptosis via protein kinase G in oestrogen receptor-positive and-negative breast cancer cell lines, FEBS J. 278 (18) (2011) 3360–3369.
[80] T. Lan, Y. Chen, J. Sang, Y. Wu, Y. Wang, L. Jiang, Y. Tao, Type II cGMP-dependent protein kinase inhibits EGF-induced MAPK/JNK signal transduction in breast cancer cells, Oncol. Rep. 27 (6) (2012) 2039–2044.
[81] T. Lan, Y. Chen, J. Sang, Y. Wu, Y. Wang, L. Jiang, Y. Tao, Type II cGMP-dependent protein kinase inhibits EGF-induced MAPK/JNK signal transduction in breast cancer cells, Oncol. Rep. 27 (6) (2012) 2039–2044.
[82] I. Arozarena, B. Sanchez-Laorden, L. Packer, C. Hidalgo-Carcedo, R. Hayward, A. Viros, R. Marais, Oncogenic BRAF induces melanoma cell invasion by down-regulating the cGMP-specific phosphodiesterase PDE5A, Cancer Cell 19 (1) (2011) 45–57.
[83] M. Fraser, S.L. Chan, S.S.L. Chan, R.R. Fiscus, B.K. Tsang, Regulation of p53 and suppression of apoptosis by the soluble guanylyl cyclase/cGMP pathway in human ovarian cancer cells, Oncogene 25 (15) (2006) 2203.
[84] K. Domek-Lopacinska, J.B. Strosznajder, Cyclic GMP metabolism and its role in brain physiology, J. Physiol. Pharmacol. 56 (2005) 15.
[85] C.A. Gruetter, B.K. Barry, D.B. McNamara, D.Y. Gruetter, P.J. Kadowitz, L. Ignarro, Relaxation of bovine coronary artery and activation of coronary arterial guanylate cyclase by nitric oxide, nitroprusside and a carcinogenic nitrosoamine, Journal of cyclic nucleotide research 5 (3) (1979) 211–224.
[86] K. Lee, A.S. Lindsey, N. Li, B. Gary, J. Andrews, A.B. Keeton, G.A. Piazza, β-Catenin nuclear translocation in colorectal cancer cells is suppressed by PDE10A inhibition, cGMP elevation, and activation of PKG, Oncotarget 7 (5) (2016) 5353.
[87] S. Ikeda, S. Kishida, H. Yamamoto, H. Murai, S. Koyama, A. Kikuchi, Axin, a negative regulator of the Wnt signaling pathway, forms a complex with GSK-3β and β-catenin and promotes GSK-3β-dependent phosphorylation of β-catenin, EMBO J. 17 (5) (1998) 1371–1384.
[88] T. Aizawa, H. Wei, J.M. Miano, J.I. Abe, B.C. Berk, C. Yan, Role of phosphodiesterase 3 in NO/cGMP-mediated antiinflammatory effects in vascular smooth muscle cells, Circ. Res. 93 (5) (2003) 406–413.
[89] A. Ataimish, N. Al-shawi, M. Al-qurtas, Evaluation of chemopreventive response of pentoxiphylline and sildenafil in colorectal carcinoma experimentally inducedin rats: comparative study with 5-fluorouracil, Int J Pharm Pharm Sci 7 (12) (2015) 217–222.
[90] N. Li, X. Chen, B. Zhu, V. Ramírez-Alcántara, J.C. Canzoneri, K. Lee, ... M.P. Moyer, Suppression of β-catenin/TCF transcriptional activity and colon tumor cell growthby dual inhibition of PDE5 and 10, Oncotarget 6 (29) (2015) 27403.
[91] B.N. Islam, S.K. Sharman, Y. Hou, A.E. Bridges, N. Singh, S. Kim, S. Sridhar, Sildenafil suppresses inflammation-driven colorectal cancer in mice, Cancer Prev. Res. 10 (7) (2017) 377–388.
[92] N. Li, K. Lee, Y. Xi, B. Zhu, B.D. Gary, V. Ramírez-Alcántara, J.T. Piazza, Phosphodiesterase 10A: a novel target for selective inhibition of colon tumor cell growth and β-catenin-dependent TCF transcriptional activity, Oncogene 34 (12) (2015) 1499.
[93] R. Feil, B. Kemp-Harper, cGMP signalling: from bench to bedside: conference on cGMP generators, effectors and therapeutic implications. EMBO reports 7 (2) (2006) 149–153.
[94] S. Schulz, M. Chinkers, D.L. Garbers, The guanylate cyclase/receptor family of proteins, FASEB J. 3 (9) (1989) 2026–2035.
[95] G. Manning, D.B. Whyte, R. Martinez, T. Hunter, S. Sudarsanam, The protein kinase complement of the human genome, Science 298 (5600) (2002) 1912–1934.
[96] S.L. Carrithers, M.T. Barber, S. Biswas, S.J. Parkinson, P.K. Park, S.D. Goldstein, S.A. Waldman, Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues, Proc. Natl. Acad. Sci. 93 (25) (1996) 14827–14832.
[97] G.S. Frick, G.M. Pitari, D.S. Weinberg, T. Hyslop, S. Schulz, S.A. Waldman, Guanylyl cyclase C: a molecular marker for staging and postoperative surveillance of patients with colorectal cancer, Expert. Rev. Mol. Diagn. 5 (5) (2005) 701–713.
[98] G.M. Pitari, P. Li, J.E. Lin, D. Zuzga, A.V. Gibbons, A.E. Snook, S.A. Waldman, The paracrine hormone hypothesis of colorectal cancer, Clinical Pharmacology & Therapeutics 82 (4) (2007) 441–447.
[99] S.A. Waldman, T. Hyslop, S. Schulz, A. Barkun, K. Nielsen, J. Haaf, ... D.S. Weinberg, Association of GUCY2C expression in lymph nodes with time to recurrence and disease-free survival in pN0 colorectal cancer, Jama 301 (7) (2009) 745–752.
[100] K.A. Steinbrecher, T.M. Tuohy, K.H. Goss, M.C. Scott, D.P. Witte, J. Groden, M.B. Cohen, Expression of guanylin is downregulated in mouse and human intestinal adenomas, Biochem. Biophys. Res. Commun. 273 (1) (2000) 225–230.
[101] E.S. Blomain, A.M. Pattison, S.A. Waldman, GUCY2C ligand replacement to prevent colorectal cancer, Cancer biology & therapy 17 (7) (2016) 713–718.
[102] S.M. Brierley, Guanylate cyclase-C receptor activation: unexpected biology, Curr. Opin. Pharmacol. 12 (6) (2012) 632–640.
[103] K.A. Lucas, G.M. Pitari, S. Kazerounian, I. Ruiz-Stewart, J. Park, S. Schulz, ... S.A. Waldman, Guanylyl cyclases and signaling by cyclic GMP, Pharmacol. Rev. 52 (3) (2000) 375–414.
[104] M. Nakazato, Guanylin family: new intestinal peptides regulating electrolyte and water homeostasis, J. Gastroenterol. 36 (4) (2001) 219–225.
[105] A.B. Vaandrager, Structure and function of the heat-stable enterotoxin receptor/guanylyl cyclase C, Mol. Cell. Biochem. 230 (1–2) (2002) 73–83.
[106] H. Danaee, T. Kalebic, T. Wyant, M. Fassan, C. Mescoli, F. Gao, M. Rugge, Consistent expression of guanylyl cyclase-C in primary and metastatic gastrointestinal cancers, PLoS One 12 (12) (2017) e0189953.
[107] J. Park, S. Schulz, J. Haaf, J.C. Kairys, S.A. Waldman, Ectopic expression of guanylyl cyclase C in adenocarcinomas of the esophagus and stomach, Cancer Epidemiology and Prevention Biomarkers 11 (8) (2002) 739–744.
[108] Y. Liu, G. Cheng, J. Qian, H. Ju, Y. Zhu, M. Stefano, ... D. Li, Expression of guanylyl cyclase C in tissue samples and the circulation of rectal cancer patients, Oncotarget 8 (24) (2017) 38841.
[109] E.S. Blomain, J.E. Lin, C.L. Kraft, U.T. Trela, J.M. Rock, A.S. Aing, S.A. Waldman, Translating colorectal cancer prevention through the guanylyl cyclase C signaling axis, Expert. Rev. Clin. Pharmacol. 6 (5) (2013) 557–564.
[110] P. Li, J.E. Lin, S. Schulz, G.M. Pitari, S.A. Waldman, Can colorectal cancer be prevented or treated by oral hormone replacement therapy? Curr. Mol. Pharmacol. 2 (3) (2009) 285–292.
[111] P. Li, J.E. Lin, I. Chervoneva, S. Schulz, S.A. Waldman, G.M. Pitari, Homeostatic control of the crypt-villus axis by the bacterial enterotoxin receptor guanylyl cyclase C restricts the proliferating compartment in intestine, Am. J. Pathol. 171 (6) (2007) 1847–1858.
[112] P. Li, S. Schulz, A. Bombonati, J.P. Palazzo, T.M. Hyslop, Y. Xu, S.A. Waldman, Guanylyl cyclase C suppresses intestinal tumorigenesis by restricting proliferation and maintaining genomic integrity, Gastroenterology 133 (2) (2007) 599–607.
[113] Lin, J. E., Li, P., Snook, A. E., Schulz, S., Dasgupta, A., Hyslop, T. M., ... & Waldman, S. A. 2010a. The hormone receptor GUCY2C suppresses intestinal tumor formation by inhibiting AKT signaling. Gastroenterology. 138(1), 241–254.
[114] Lin, J. E., Li, P., Snook, A. E., Schulz, S., Dasgupta, A., Hyslop, T. M., ... & Waldman, S. A. 2010b. The hormone receptor GUCY2C suppresses intestinal tumor formation by inhibiting AKT signaling. Gastroenterology. 138(1), 241–254.
[115] N. Basu, S. Saha, I. Khan, S.G. Ramachandra, S.S. Visweswariah, Intestinal cell proliferation and senescence are regulated by receptor guanylyl cyclase C and p21, J. Biol. Chem. 289 (1) (2014) 581–593.
[116] L.M. Coussens, B. Fingleton, L.M. Matrisian, Matrix metalloproteinase inhibitors and cancer—trials and tribulations, Science 295 (5564) (2002) 2387–2392.
[117] R. Fridman, M. Toth, I. Chvyrkova, S.O. Meroueh, S. Mobashery, Cell surface association of matrix metalloproteinase-9 (gelatinase B), Cancer Metastasis Rev. 22 (2–3) (2003) 153–166.
[118] W.J. Lubbe, D.S. Zuzga, Z. Zhou, W. Fu, J. Pelta-Heller, R.J. Muschel, G.M. Pitari, Guanylyl cyclase C prevents colon cancer metastasis by regulating tumor epithelial cell matrix metalloproteinase-9, Cancer Res. 69 (8) (2009) 3529–3536.
[119] R. Birbe, J.P. Palazzo, R. Walters, D. Weinberg, S. Schulz, S.A. Waldman, Guanylyl cyclase C is a marker of intestinal metaplasia, dysplasia, and adenocarcinoma of the gastrointestinal tract, Hum. Pathol. 36 (2) (2005) 170–179.
[120] S. Schulz, T. Hyslop, J. Haaf, C. Bonaccorso, K. Nielsen, M.E. Witek, S.A. Waldman, A validated quantitative assay to detect occult micrometastases by reverse transcriptase-polymerase chain reaction of guanylyl cyclase C in patients with colorectal cancer, Clin. Cancer Res. 12 (15) (2006) 4545–4552.
[121] M.E. Witek, K. Nielsen, R. Walters, T. Hyslop, J. Palazzo, S. Schulz, S.A. Waldman, The putative tumor suppressor Cdx2 is overexpressed by human colorectal adenocarcinomas, Clin. Cancer Res. 11 (24) (2005) 8549–8556.
[122] T. Hyslop, D.S. Weinberg, S. Schulz, A. Barkun, S.A. Waldman, Analytic lymph node number establishes staging accuracy by occult tumor burden in colorectal cancer, J. Surg. Oncol. 106 (1) (2012) 24–30.
[123] D.S. Weinberg, J.E. Lin, N.R. Foster, G. Della'Zanna, A. Umar, D. Seisler, S.A. Waldman, Bioactivity of oral linaclotide in human colorectum for cancer chemoprevention, Cancer Prev. Res. 10 (6) (2017) 345–354.
[124] M. Conti, S.L.C. Jin, The molecular biology of cyclic nucleotide phosphodiesterases, Progress in Nucleic Acid Research and Molecular Biology, vol. 63, Academic Press, 1999, pp. 1–38.
[125] R. Hoffmann, G.S. Baillie, S.J. MacKenzie, S.J. Yarwood, M.D. Houslay, The MAP kinase ERK2 inhibits the cyclic AMP-specific phosphodiesterase HSPDE4D3 by phosphorylating it at Ser579, EMBO J. 18 (4) (1999) 893–903.
[126] S.J. MacKenzie, G.S. Baillie, I. McPhee, C. MacKenzie, R. Seamons, T. McSorley, M.D. Houslay, Long PDE4 cAMP specific phosphodiesterases are activated by protein kinase A-mediated phosphorylation of a single serine residue in Upstream Conserved Region 1 (UCR1), Br. J. Pharmacol. 136 (3) (2002) 421–433.
[127] R.W. Butcher, E.W. Sutherland, Adenosine 3′, 5′-phosphate in biological materials, J. Biol. Chem. 237 (7) (1962) 1244–1250.
[128] H. Ke, H. Wang, Crystal structures of phosphodiesterases and implications on

substrate specificity and inhibitor selectivity, Curr. Top. Med. Chem. 7 (4) (2007) 391–403.
[129] H. Wang, M.S. Peng, Y. Chen, J. Geng, H. Robinson, M.D. Houslay, H. Ke, Structures of the four subfamilies of phosphodiesterase-4 provide insight into the selectivity of their inhibitors, Biochem. J. 408 (2) (2007) 193–201.
[130] S. Mikami, S. Sasaki, Y. Asano, O. Ujikawa, S. Fukumoto, K. Nakashima, T. Taniguchi, Discovery of an orally bioavailable, brain-penetrating, in vivo active Phosphodiesterase 2A inhibitor lead series for the treatment of cognitive disorders, J. Med. Chem. 60 (18) (2017) 7658–7676.
[131] A.P. Nayak, D.A. Deshpande, R.B. Penn, New targets for resolution of airway remodeling in obstructive lung diseases, F1000Research 7 (2018).
[132] J. Huber, G.G. Krueger, J.E. Hawkes, Phosphodiesterase (PDE) inhibitors for the treatment of inflammatory skin conditions, Biologic and Systemic Agents in Dermatology, Springer, Cham, 2018, pp. 209–219.
[133] M. Thieme, S.H. Sivritas, E. Mergia, S.A. Potthoff, G. Yang, L. Hering, ... J. Stegbauer, Phosphodiesterase 5 inhibition ameliorates angiotensin II-dependent hypertension and renal vascular dysfunction, American Journal of Physiology-Renal Physiology 312 (3) (2017) F474–F481.
[134] M. Benej, X. Hong, S. Vibhute, S. Scott, J. Wu, E. Graves, S.C. Chen, Papaverine and its derivatives radiosensitize solid tumors by inhibiting mitochondrial metabolism, Proc. Natl. Acad. Sci. 115 (42) (2018) 10756–10761.
[135] L. Favot, T. Keravis, C. Lugnier, Modulation of VEGF-induced endothelial cell cycle protein expression through cyclic AMP hydrolysis by PDE2 and PDE4, Thromb. Haemost. 92 (09) (2004) 634–645.
[136] J.T. Lim, G.A. Piazza, E.K.H. Han, T.M. Delohery, H. Li, T.S. Finn, P.H. Gross, Sulindac derivatives inhibit growth and induce apoptosis in human prostate cancer cell lines, Biochem. Pharmacol. 58 (7) (1999) 1097–1107.
[137] G.A. Piazza, A.K. Rahm, T.S. Finn, B.H. Fryer, H. Li, A.L. Stoumen, ... D.J. Ahnen, Apoptosis primarily accounts for the growth-inhibitory properties of sulindac metabolites and involves a mechanism that is independent of cyclooxygenase inhibition, cell cycle arrest, and p53 induction, Cancer Res. 57 (12) (1997) 2452–2459.
[138] W.J. Thompson, G.A. Piazza, H. Li, L. Liu, J. Fetter, B. Zhu, ... R. Pamukcu, Exisulind induction of apoptosis involves guanosine 3′, 5′-cyclic monophosphate phosphodiesterase inhibition, protein kinase G activation, and attenuated β-catenin, Cancer Res. 60 (13) (2000) 3338–3342.
[139] J.M. Seeling, J.R. Miller, R. Gil, R.T. Moon, R. White, D.M. Virshup, Regulation of β-catenin signaling by the B56 subunit of protein phosphatase 2A, Science 283 (5410) (1999) 2089–2091.
[140] H. Yamamoto, S. Kishida, M. Kishida, S. Ikeda, S. Takada, A. Kikuchi, Phosphorylation of axin, a Wnt signal negative regulator, by glycogen synthase kinase-3β regulates its stability, J. Biol. Chem. 274 (16) (1999) 10681–10684.
[141] M. Conti, J. Beavo, Biochemistry and physiology of cyclic nucleotide phosphodiesterases: essential components in cyclic nucleotide signaling, Annu. Rev. Biochem. 76 (2007) 481–511.
[142] M.A. Feijge, K. Ansink, K. Vanschoonbeek, J.W. Heemskerk, Control of platelet activation by cyclic AMP turnover and cyclic nucleotide phosphodiesterase type-3, Biochem. Pharmacol. 67 (8) (2004) 1559–1567.
[143] M.J. Leroy, E. Degerman, M. Taira, T. Murata, L.H. Wang, M.A. Movsesian, V.C. Manganiello, Characterization of two recombinant PDE3 (cGMP-inhibited cyclic nucleotide phosphodiesterase) isoforms, RcGIP1 and HcGIP2, expressed in NIH 3006 murine fibroblasts and Sf9 insect cells, Biochemistry 35 (31) (1996) 10194–10202.
[144] M. Taira, S.C. Hockman, J.C. Calvo, P. Belfrage, V.C. Manganiello, Molecular cloning of the rat adipocyte hormone-sensitive cyclic GMP-inhibited cyclic nucleotide phosphodiesterase, J. Biol. Chem. 268 (25) (1993) 18573–18579.
[145] Dawson, D. L., Cutler, B. S., Meissner, M. H., & Strandness Jr, D. E. 1998. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. Circulation. 98(7), 678–686.
[146] E.M. Sorkin, A. Markham, Cilostazol, Drugs Aging 14 (1) (1999) 63–71.
[147] G. Grignani, G.A. Jamieson, Platelets in tumor metastasis: generation of adenosine diphosphate by tumor cells is specific but unrelated to metastatic potential, Blood 71 (4) (1988) 844–849.
[148] Y. Ikeda, T. Matsumata, K. Takenaka, M. Yamagata, K. Sugimachi, Effects of doxorubicin and/or cilostazol on cancer cells during liver regeneration after two-thirds hepatectomy in rats, Oncology 55 (4) (1998) 354–356.
[149] Murata, K., Kameyama, M., Fukui, F., Ohigashi, H., Hiratsuka, M., Sasaki, Y., ... & Ishikawa, O. 1999. Phosphodiesterase type III inhibitor, cilostazol, inhibits colon cancer cell motility. Clinical & experimental metastasis. 17(6), 525–530.
[150] T. Tsukahara, Y. Matsuda, H. Haniu, Cyclic phosphatidic acid stimulates cAMP production and inhibits growth in human colon cancer cells, PLoS One 8 (11) (2013) e81139.
[151] T. Kitamura, Y. Kitamura, S. Kuroda, Y. Hino, M. Ando, K. Kotani, M. Kasuga, Insulin-induced phosphorylation and activation of cyclic nucleotide phosphodiesterase 3B by the serine-threonine kinase Akt, Mol. Cell. Biol. 19 (9) (1999) 6286–6296.
[152] G. Bolger, T. Michaeli, T. Martins, T. St John, B. Steiner, L. Rodgers, K. Ferguson, A family of human phosphodiesterases homologous to the dunce learning and memory gene product of Drosophila melanogaster are potential targets for antidepressant drugs, Mol. Cell. Biol. 13 (10) (1993) 6558–6571.
[153] B.J. Lipworth, Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease, Lancet 365 (9454) (2005) 167–175.
[154] K. Shailubhai, H.Y. Helen, K. Karunanandaa, J.Y. Wang, S.L. Eber, Y. Wang, ... S.S. Boddupalli, Uroguanylin treatment suppresses polyp formation in the ApcMin/+ mouse and induces apoptosis in human colon adenocarcinoma cells via cyclic GMP, Cancer Res. 60 (18) (2000) 5151–5157.
[155] B.M. Schmidt, M. Kusma, M. Feuring, W.E. Timmer, M. Neuhäuser, T. Bethke, M. Wehling, The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis, J. Allergy Clin. Immunol. 108 (4) (2001) 530–536.
[156] E. Zeller, H.J. Stief, B. Pflug, M. Sastre-y-Hernandez, Results of a phase II study of the antidepressant effect of rolipram, Pharmacopsychiatry 17 (06) (1984) 188–190.
[157] A.B. Gottlieb, B. Strober, J.G. Krueger, P. Rohane, J.B. Zeldis, C.C. Hu, C. Kipnis, An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast, Curr. Med. Res. Opin. 24 (5) (2008) 1529–1538.
[158] T. Tsunoda, T. Ota, T. Fujimoto, K. Doi, Y. Tanaka, Y. Yoshida, ... M. Kuroki, Inhibition of phosphodiesterase-4 (PDE4) activity triggers luminal apoptosis and AKT dephosphorylation in a 3-D colonic-crypt model, Mol. Cancer 11 (1) (2012) 46.
[159] A. Marquette, J. André, M. Bagot, A. Bensussan, N. Dumaz, ERK and PDE4 cooperate to induce RAF isoform switching in melanoma, Nat. Struct. Mol. Biol. 18 (5) (2011) 584.
[160] S.W. Kim, D. Rai, M.R. McKeller, R.C. Aguiar, Rational combined targeting of phosphodiesterase 4B and SYK in DLBCL, Blood 113 (24) (2009) 6153–6160.
[161] P.G. Smith, F. Wang, K.N. Wilkinson, K.J. Savage, U. Klein, D.S. Neuberg, ... R.C. Aguiar, The phosphodiesterase PDE4B limits cAMP-associated PI3K/AKT–dependent apoptosis in diffuse large B-cell lymphoma, Blood 105 (1) (2005) 308–316.
[162] T.C. Chen, P. Wadsten, S. Su, N. Rawlinson, F.M. Hofman, C.K. Hill, A.H. Schonthal, The type IV phosphodiesterase inhibitor rolipram induces expression inhibitors p21Cip1 and p27Kip1, resulting in growth inhibition, increased differentiation, and subsequent apoptosis of malignant A-172 glioma cells, Cancer biology & therapy 1 (3) (2002) 268–276.
[163] S. Gong, Y. Chen, F. Meng, Y. Zhang, H. Wu, F. Wu, Roflumilast restores cAMP/PKA/CREB signaling axis for FtMt-mediated tumor inhibition of ovarian cancer, Oncotarget 8 (68) (2017) 112341.
[164] R. Sengupta, T. Sun, N.M. Warrington, J.B. Rubin, Treating brain tumors with PDE4 inhibitors, Trends Pharmacol. Sci. 32 (6) (2011) 337–344.
[165] C.D. Yeo, Y.A. Kim, H.Y. Lee, J.W. Kim, S.J. Kim, S.H. Lee, Y.K. Kim, Roflumilast treatment inhibits lung carcinogenesis in benzo (a) pyrene-induced murine lung cancer model, Eur. J. Pharmacol. 812 (2017) 189–195.
[166] T. Ota, K. Doi, T. Fujimoto, Y. Tanaka, M. Ogawa, H. Matsuzaki, ... T. Tsunoda, KRAS up-regulates the expression of miR-181a, miR-200c and miR-210 in a three-dimensional-specific manner in DLD-1 colorectal cancer cells, Anticancer Res. 32 (6) (2012) 2271–2275.
[167] T. Tsunoda, S. Ishikura, K. Doi, H. Matsuzaki, Y. Iwaihara, S. Shirasawa, Resveratrol induces luminal apoptosis of human colorectal cancer HCT116 cells in three-dimensional culture, Anticancer Res. 34 (8) (2014) 4551–4555.
[168] E. Bandrés, R. Malumbres, E. Cubedo, B. Honorato, R. Zarate, A. Labarga, J. García-Foncillas, A gene signature of 8 genes could identify the risk of recurrence and progression in Dukes' B colon cancer patients, Oncol. Rep. 17 (5) (2007) 1089–1094.
[169] K. Murata, T. Sudo, M. Kameyama, H. Fukuoka, M. Mukai, Y. Doki, ... S. Imaoka, Cyclic AMP specific phosphodiesterase activity and colon cancer cell motility, Clinical & experimental metastasis 18 (7) (2000) 599–604.
[170] P.H. Schafer, A. Parton, L. Capone, D. Cedzik, H. Brady, J.F. Evans, ... R. Chopra, Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity, Cellular signaling 26 (9) (2014) 2016–2029.
[171] G. Schett, V.S. Sloan, R.M. Stevens, P. Schafer, Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases, Therapeutic advances in musculoskeletal disease 2 (5) (2010) 271–278.
[172] F.E. McCann, A.C. Palfreeman, M. Andrews, D.P. Perocheau, J.J. Inglis, P. Schafer, F.M. Brennan, Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis, Arthritis research & therapy 12 (3) (2010) R107.
[173] K. Nishi, H. Luo, S. Ishikura, K. Doi, Y. Iwaihara, L. Wills, ... T. Tsunoda, Apremilast induces apoptosis of human colorectal cancer cells with mutant KRAS, Anticancer Res. 37 (7) (2017) 3833–3839.
[174] S.J. Park, F. Ahmad, A. Philp, K. Baar, T. Williams, H. Luo, M.K. Kim, Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases, Cell 148 (3) (2012) 421–433.
[175] S.X. Yuan, D.X. Wang, Q.X. Wu, C.M. Ren, Y. Li, Q.Z. Chen, P. Zhang, BMP9/p38 MAPK is essential for the antiproliferative effect of resveratrol on human colon cancer, Oncol. Rep. 35 (2) (2016) 939–947.
[176] M.P. Fuggetta, G. Lanzilli, M. Tricarico, A. Cottarelli, R. Falchetti, G. Ravagnan, E. Bonmassar, Effect of resveratrol on proliferation and telomerase activity of human colon cancer cells in vitro, Journal of Experimental and Clinical Cancer Research 25 (2) (2006) 189.
[177] Hope, C., Planutis, K., Planutiene, M., Moyer, M. P., Johal, K. S., Woo, J., ... & Holcombe, R. F. 2008. Low concentrations of resveratrol inhibit Wnt signal throughput in colon-derived cells: implications for colon cancer prevention. Mol. Nutr. Food Res.. 52(S1), S52-S61.
[178] Y.C. Liang, S.H. Tsai, L. Chen, S.Y. Lin-Shiau, J.K. Lin, Resveratrol-induced G2 arrest through the inhibition of CDK7 and p34CDC2 kinases in colon carcinoma HT29 cells, Biochem. Pharmacol. 65 (7) (2003) 1053–1060.
[179] J. Vanamala, L. Reddivari, S. Radhakrishnan, C. Tarver, Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways, BMC Cancer 10 (1) (2010) 238.

[180] Y. Schneider, F. Vincent, B. Duranton, L. Badolo, F. Gossé, C. Bergmann, F. Raul, Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells, Cancer Lett. 158 (1) (2000) 85–91.
[181] S. Ulrich, S.M. Loitsch, O. Rau, A. von Knethen, B. Brüne, M. Schubert-Zsilavecz, J.M. Stein, Peroxisome proliferator–activated receptor γ as a molecular target of resveratrol-induced modulation of polyamine metabolism, Cancer Res. 66 (14) (2006) 7348–7354.
[182] F. Wolter, B. Akoglu, A. Clausnitzer, J. Stein, Downregulation of the cyclin D1/Cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines, J. Nutr. 131 (8) (2001) 2197–2203.
[183] D. Delmas, P. Passilly-Degrace, B. Jannin, M.C. Malki, N. Latruffe, Resveratrol, a chemopreventive agent, disrupts the cell cycle control of human SW480 colorectal tumor cells, Int. J. Mol. Med. 10 (2) (2002) 193–199.
[184] G. Kroemer, L. Galluzzi, C. Brenner, Mitochondrial membrane permeabilization in cell death, Physiol. Rev. 87 (1) (2007) 99–163.
[185] N.F. Trincheri, G. Nicotra, C. Follo, R. Castino, C. Isidoro, Resveratrol induces cell death in colorectal cancer cells by a novel pathway involving lysosomal cathepsin D, Carcinogenesis 28 (5) (2006) 922–931.
[186] K.J. Woo, T.J. Lee, S.H. Lee, J.M. Lee, J.H. Seo, Y.J. Jeong, T.K. Kwon, Elevated gadd153/chop expression during resveratrol-induced apoptosis in human colon cancer cells, Biochem. Pharmacol. 73 (1) (2007) 68–76.
[187] D. Colin, E. Limagne, S. Jeanningros, A. Jacquel, G. Lizard, A. Athias, D. Delmas, Endocytosis of resveratrol via lipid rafts and activation of downstream signaling pathways in cancer cells, Cancer Prev. Res. 4 (7) (2011) 1095–1106.
[188] Y.Z. Liu, K. Wu, J. Huang, Y. Liu, X. Wang, Z.J. Meng, ... L.J. Yin, The PTEN/PI3K/Akt and Wnt/β-catenin signaling pathways are involved in the inhibitory effect of resveratrol on human colon cancer cell proliferation, Int. J. Oncol. 45 (1) (2014) 104–112.
[189] I. Alfaras, M.E. Juan, J.M. Planas, trans-Resveratrol reduces precancerous colonic lesions in dimethylhydrazine-treated rats, J. Agric. Food Chem. 58 (13) (2010) 8104–8110.
[190] L.A. Stivala, M. Savio, F. Carafoli, P. Perucca, L. Bianchi, G. Maga, V. Vannini, Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol, J. Biol. Chem. 276 (25) (2001) 22586–22594.
[191] L. Tessitore, A. Davit, I. Sarotto, G. Caderni, Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21 CIP expression, Carcinogenesis 21 (8) (2000) 1619–1622.
[192] M. Sengottuvelan, K. Deeptha, N. Nalini, Influence of dietary resveratrol on early and late molecular markers of 1, 2-dimethylhydrazine–induced colon carcinogenesis, Nutrition 25 (11 – 12) (2009) 1169–1176.
[193] M. Sengottuvelan, R. Senthilkumar, N. Nalini, Modulatory influence of dietary resveratrol during different phases of 1, 2-dimethylhydrazine induced mucosal lipid-peroxidation, antioxidant status and aberrant crypt foci development in rat colon carcinogenesis, Biochimica et Biophysica Acta (BBA)-General Subjects 1760 (8) (2006) 1175–1183.
[194] Y. Schneider, B. Duranton, F. Goss, R. Schleiffer, N. Seiler, F. Raul, Resveratrol inhibits intestinal tumorigenesis and modulates host-defense-related gene expression in an animal model of human familial adenomatous polyposis, Nutr. Cancer 39 (1) (2001) 102–107.
[195] C.C. Ziegler, L. Rainwater, J. Whelan, M.F. McEntee, Dietary resveratrol does not affect intestinal tumorigenesis in Apc Min/+ mice, J. Nutr. 134 (1) (2004) 5–10.
[196] W.A. Hammond, A. Swaika, K. Mody, Pharmacologic resistance in colorectal cancer: a review, Therapeutic advances in medical oncology 8 (1) (2016) 57–84.
[197] I. Sansal, W.R. Sellers, The biology and clinical relevance of the PTEN tumor suppressor pathway, J. Clin. Oncol. 22 (14) (2004) 2954–2963.
[198] V. Stambolic, A. Suzuki, J.L. De La Pompa, G.M. Brothers, C. Mirtsos, T. Sasaki, T.W. Mak, Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN, Cell 95 (1) (1998) 29–39.
[199] K.A. Hanson, J.W. Ziegler, S.D. Rybalkin, J.W. Miller, S.H. Abman, W.R. Clarke, Chronic pulmonary hypertension increases fetal lung cGMP phosphodiesterase activity, Am. J. Phys. Lung Cell. Mol. Phys. 275 (5) (1998) L931–L941.
[200] L. Pusztai, J.H. Zhen, B. Arun, E. Rivera, C. Whitehead, W.J. Thompson, D. Booser, Phase I and II study of exisulind in combination with capecitabine in patients with metastatic breast cancer, J. Clin. Oncol. 21 (18) (2003) 3454–3461.
[201] H.N. Tinsley, B.D. Gary, J. Thaiparambil, N. Li, W. Lu, Y. Li, G.A. Piazza, Colon tumor cell growth–inhibitory activity of sulindac sulfide and other nonsteroidal anti-inflammatory drugs is associated with phosphodiesterase 5 inhibition, Cancer Prev. Res. 3 (10) (2010) 1303–1313.
[202] C.N. Bernstein, J.F. Blanchard, E. Kliewer, A. Wajda, Cancer risk in patients with inflammatory bowel disease: a population-based study, Cancer 91 (4) (2001) 854–862.
[203] A.L.O. Hebb, H.A. Robertson, E.M. Denovan-Wright, Striatal phosphodiesterase mRNA and protein levels are reduced in Huntington' s disease transgenic mice prior to the onset of motor symptoms, Neuroscience 123 (4) (2004) 967–981.
[204] K.P.1 Raj, J.A. Zell, C.L. Rock, C.E. McLaren, C. Zoumas-Morse, E.W. Gerner, F.L. Meyskens, Role of dietary polyamines in a phase III clinical trial of difluoromethylornithine (DFMO) and sulindac for prevention of sporadic colorectal adenomas, Br. J. Cancer 108 (3) (2013) 512–518.
[205] A.V.1 Nguyen, M. Martinez, M.J. Stamos, M.P. Moyer, K. Planutis, C. Hope, R.F. Holcombe, Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer, Cancer Manag Res. 1 (2009) 25–37.
[206] N.J. Samadder, D.W. Neklason, K.M. Boucher, K.R. Byrne, P. Kanth, W. Samowitz, D. Jones, S.V. Tavtigian, M.W. Done, T. Berry, K. Jasperson, L. Pappas, L. Smith, D. Sample, R. Davis, M.K. Topham, P. Lynch, E. Strait, W. McKinnon, R.W. Burt, S.K. Kuwada, Effect of Sulindac and Erlotinib vs Placebo on Duodenal Neoplasia in Familial Adenomatous Polyposis: A Randomized Clinical Trial, JAMA 315 (12) (2016) 1266–1275.
[207] M. Wu, Y. Wu, T. Lan, L. Jiang, H. Qian, Y. Chen, Type II cGMP-dependent protein kinase inhibits EGF-induced JAK/STAT signaling in gastric cancer cells, Mol. Med. Rep. 14 (2) (2016) 1849–1856.