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REVIEW ARTICLE

PI3K/ Akt/ mTOR Pathway as a Therapeutic Target for Colorectal Cancer: A Review of Preclinical and Clinical Evidence

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Abstract: ***Background*:** Phosphoinositide 3-kinase (PI3Ks) is a member of intracellular lipid kinases and involved in the regulation of cellular proliferation, differentiation and survival. Overexpression of the PI3K/Akt/mTOR signalling has been reported in various forms of cancers, especially in colorectal cancers (CRC). Due to their significant roles in the initiation and progression events of colorectal cancer, they are recognized as a striking therapeutic target.

***Objective*:** The present review is aimed to provide a detailed outline on the role of PI3K/Akt/mTOR pathway in the initiation and progression events of colorectal cancers as well as its function in drug resistance. Further, the role of PI3K/Akt/mTOR inhibitors alone and in combination with other chemotherapeutic drugs, in alleviating colorectal cancer is also discussed. The review contains preclinical and clinical evidence as well as patent literature of the pathway inhibitors which are natural and synthetic in origin.

***Methods*:** The data were obtained from PubMed/Medline databases, Scopus and Google patent literature.

***Results*:** PI3K/Akt/mTOR signalling is an important event in colorectal carcinogenesis. In addition, it plays significant roles in acquiring drug resistance as well as metastatic initiation events of CRCs. Several small molecules of natural and synthetic origin have been found to be potent inhibitors of CRCs by effectively downregulating the pathway. Data from various clinical studies also support these pathway inhibitors and several among them are patented.

***Conclusion*:** Inhibitors of the PI3K/mTOR pathway have been successful for the treatment of primary and metastatic colorectal cancers, rendering the pathway as a promising clinical cancer therapeutic target.

Keywords: Anticancer activity, metastasis, PI3K pathway, natural products, colon cancer, synthetic inhibitors.

1. INTRODUCTION

Phosphoinositide 3-kinase or phosphatidylinositol-3 kinase (PI3Ks) belongs to a broad class of intracellular lipid kinases; which are responsible for the phosphorylation of a variety of enzymes. The PI3K has been initially described by Cantley [1] in the early 1980s; together with their downstream signalling factors such as protein kinase B (Akt) and mechanistic target of rapamycin (mTOR) (Fig. **1**) [2]. The PI3K/Akt/mTOR pathway has been involved in the regulation of physiological processes such as cell proliferation and survival, adhesion, as well as cellular motility. Apart from their physiological roles, the pathway has been involved in several pathological processes including cancers of the colon [3], breast [4], liver [5] and pancreas [6].

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Overexpression of the PI3K/Akt/mTOR signalling has been reported in different forms of colorectal cancers (CRC). Due to the roles in the initiation and progression events of cancers including metastasis, drug resistance and cancer stemness, the PI3K/Akt/mTOR pathway has emerged as a potential therapeutic target for colorectal cancers. The present review thus aims to provide a detailed outline on the association of PI3K/Akt/mTOR signalling in colon cancer and use of various synthetic and natural inhibitors of this pathway as a drug candidate against colorectal cancers.

2. PI3K/ Akt/ mTOR SIGNALLING AND ITS ASSOCIATION WITH VARIOUS CANCERS

The signalling of PI3K/Akt/mTOR pathway is under the control of a master lipid kinase, 3-phosphoinositide-dependent protein kinase-1 (PDK-1), which is known to interact with cytosolic lipids. The binding of PDPK1 induces the activation of various downstream kinases including Akt, PKC, S6K (Ribosomal protein S6 kinase beta-1) and SGK (a serine-threonine protein kinase).

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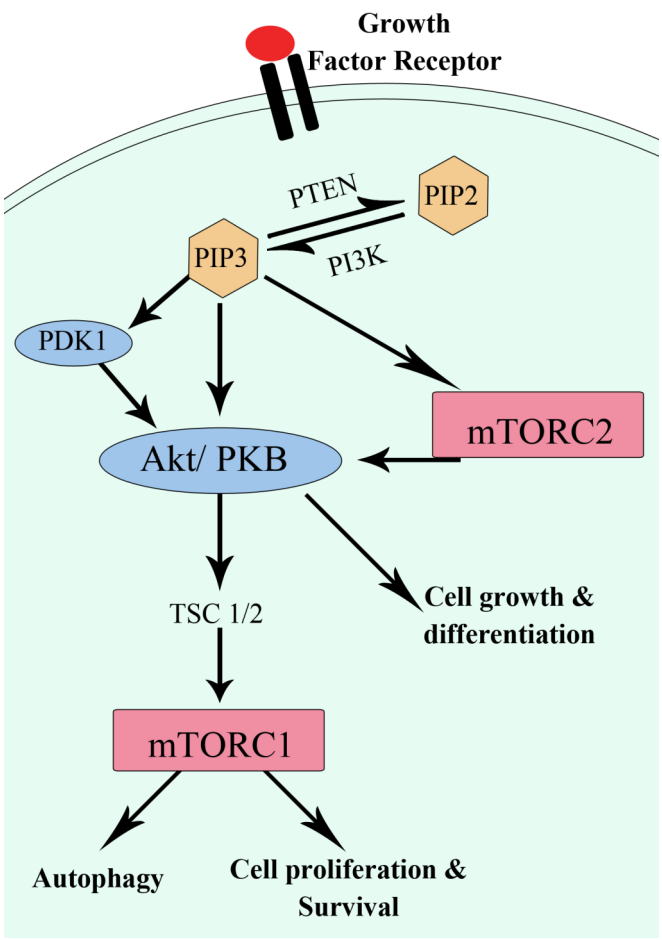

Fig. (1). Regulation and physiological roles of the PI3K/Akt/mTOR pathway.

In glioblastoma, the PI3K signalling act as a pro-survival factor [7] and inhibition of which inhibits glioma progression [8, 9]. Apart from the glioma and glioblastoma, PI3K signalling has also found to be upregulated in the breast cancer progression [10]. In addition, PI3K inhibitors found to successfully reduce the incidence of triple negative and estrogen receptor positive breast cancers [11-13]. Activation of mTORC2 together with PTEN suppression is commonly observed in HCC [14, 15]; under such conditions, conventional anti-microtubule agents has shown to reduce the progression of HCC in a PI3K dependent manner [16, 17]. In Lymphoma; overexpression of PI3K/Akt/mTOR signalling is associated with increased aggressiveness [18, 19]. Clinical studies have also shown a positive association of Germinal Center B-Cell-like Diffuse Large B-Cell Lymphoma with increased genetic alterations in the PI3K-AKT pathway [20]. Apart from the cancer initiation events, PI3K/Akt/mTOR signalling confers resistance for prostate cancer cells against androgen deprivation therapy [21, 22]. In addition, Festuccia [23] has reported that inhibition of the PI3K signalling reduces Prostate cancer progression. PI3K/Akt/mTOR has also been associated with the aggressiveness in Head and neck cancer [24-26] and lung cancer [27, 28]. The association of various cancers with PI3K axis is listed in (Table **1**).

3. PI3K/ Akt/ mTOR SIGNALING IN COLORECTAL CARCINOGENESIS

In colorectal cancers, the predominant genetic changes include the overexpression of Insulin-like growth factor, KRAS mutations, diminished or mutated PTEN functioning and PI3K mutations. The PI3K/Akt/mTOR signaling has significant roles in the colon epithelial cells; it modulates the cellular responses to glucose and various amino acids as well as response to various extracellular signals. Studies confirmed the role of Akt in colon cancer by suppressing different isoforms Akt1 & Akt2, which showed reduced tumor growth. Further, the study claimed that Akt activation is mainly mediated through FOXO, rather than mTOR [32].

PI3K- mTOR functioning is important for survival and multiplication of colon cancer cells [29]; together with the PI3K signaling, p85α, Akt, and p70 overexpression has exacerbated the progression of colon cancer [30, 31]. In addition, Akt signaling promotes epithelial-mesenchymal transition (EMT) and subsequently increase tumor growth [33] in colon cancer cells pose the risk of metastasis [34]. *Doublecortin-like kinase 1* (DCLK1) is an oncogene that activates EMT mediated through PI3K/Akt/Sp1 dependent NF-κBp65 expression [35]; the up-regulation of DCLK1 has an important role in the metastasis, stemness and poor prognosis of colorectal cancers *via* induction of EMT [36, 37]. *G protein-coupled receptor 56* (GPR56) is another oncogene upregulated considerably in colon cancers and is known to be involved in the activation of the EMT process in a PI3K/Akt dependent manner. *Tripartite motif-containing 59* (TRIM59) is also involved in the EMT associated changes and its metastatic conversion in colon cancer patients [38]; the experimental knockdown of which has been shown to inhibit the metastatic cascades in colon cancer cells [39].

In connection with these reports, studies have been reported that *milk fat globule epidermal growth factor-8* (MFG-E8) [40], *sine oculis homeobox 4* (SIX4) [41] and *WD repeat-containing protein 5* (WDR5) [42] promote colon cancer metastasis in a PI3K-Akt dependent manner. Apart from cancer metastasis, PI3K axis is also involved in the chemotherapy resistance in colon cancer cells. Increased expression of Nectin4, a Ca2+-independent cellular adhesion molecule, has been associated with PI3K-Akt signaling and subsequently leading to the resistance against 5-Fluorouracil [43]. Later, Wang, Wang [44] has shown that the overexpression of *Metastasis-associated colon cancer 1* (MACC1) gene also increases the resistance against 5-FU and induction of cancer stem cell (CSC) like properties in colon cancer cells. In colon cells, expression of *Deleted in breast cancer* (DBC1) is associated with the expression of MACC1 and finally leading to the metastatic conversion [45]. *Cellular prion protein* (PrP^C), another oncogenic protein, has shown to increase the colon cancer cell survival and proliferation mediated through the PI3K-Akt pathway and by modulating cell cycle-associated proteins [46]. Micro RNAs also play important role in colon cancer by regulating PI3K pathway; microRNA-135b and microRNA-182 have been shown to mediate the carcinogenesis, invasiveness and 5FU resistance *via* ST6GALNAC2 associated PI3K/AKT Pathway activation [47, 48]. Further, miR-26a together with long non-coding RNA (LINC01296) and mucin 1 promotes the pro-

Table 1. Association of PI3K/Akt/mTOR signalling with various cancers.

Type of Cancer	Effect	References
Glioblastoma	PI3K act as a pro-survival factor	[7]
Glioma	Inhibition of PI3K inhibits glioma progression	[8]
Glioblastoma	Inhibition of glioblastoma by PI3K inhibitors	[9]
Triple negative breast cancer	Inhibitors of PI3K in TNBC	[11]
Breast cancer	PI3K activation in the breast cancer progression	[10]
Breast cancer	PI3K inhibitors prevent breast cancer proliferation	[12, 13]
Hepatocellular carcinoma	Conventional chemotherapeutic agents or antimicrotubule agents inhibit HCC growth	[16, 17]
Hepatocellular carcinoma	The loss of PTEN promotes HCC *via* the mTORC2 pathway	[14, 15]
Colon cancer	mTOR pathway activation increases cell viability	[29]
Colon cancer	p85α, Akt, mTOR and p70 overexpression induce colon cancer progression	[30, 31]
Lymphoma	PI3K/Akt/mTOR activation induces aggressiveness in lymphoma	[18, 19]
Prostate cancer	PI3K/Akt/mTOR is associated with androgen deprivation therapy resistance	[21, 22]
Prostate cancer	Targeting of the PI3K signaling reduces cancer progression	[23]
Head and neck cancer	PI3K/Akt/mTOR pathway alterations increase aggressiveness	[24-26]
Lung cancer	PI3K signaling is upregulated in lung cancers and therapeutic intervention inhibiting cancer	[27, 28]

gression and metastasis of colon cancer in mice xenograft models [49]. Studies by Liang, Gao [50] have revealed that miR-125a-3p together with *fucosyltransferase 5 & 6* (FUT-5 & FU-6) promotes colon cancer angiogenesis and invasion. In xenograft mice models of colon cancer, the expression of *Inosine 5'-monophosphate dehydrogenase type II* (IMPDH2) has shown to induce colorectal cancer progression through the regulation of PI3K/AKT/mTOR/FOXO1 signaling [51].

4. SYNTHETIC INHIBITORS OF PI3K/ Akt/ mTOR SIGNALING IN COLON CANCER

Due to their multiple roles in colon carcinogenesis, PI3K/Akt/mTOR pathway has emerged as a promising therapeutic target. The scientific community has made sincere attempts to interfere with this pathway so as to control the progression of colon cancer. Numerous inhibitors of the PI3K/Akt pathway have been developed and are being used as a promising drug candidate against colon cancer.

Among the clinically used drugs, Metformin has been shown to inhibit the proliferation of colon cancer cells by inhibiting Myc protein synthesis *via* mTOR dependent eIF4E signaling [52]. Diclofenac, an anti-inflammatory drug, has been shown to induce the de-phosphorylation of PTEN & Akt, thereby inhibiting cell survival in HCT-116 [53]. Inositol hexaphosphate (InsP6) or phytic acid is a naturally occurring poly-phosphorylated carbohydrate, reported having anticancer activity against a wide variety of cancer cells including that of the colon. It has been observed that the InsP6 induce apoptosis in a PI3K dependent manner by downregulating the expression of Akt/mTOR signalling [54]. Tetra-arsenic hexoxide, which is widely used in Korean medicinal systems, is also shown to possess anticancer activity against colon cancer cell (SW480) in a PI3K driven p38/MAPK dependent manner [55]. Later, Liu, Gao [56] observed that Catalpol, an iridoid glycoside, reduced cell viability in colon cancer cell- HCT116 *via* microRNA-200 and also by down-regulating the expression of PI3K-Akt signaling. Tandutinib is an inhibitor of the c-kit gene which is actively involved in the invasive changes of colon cancers, has shown to reduce the rate of proliferation of colon cancer cells. The drug also prevented the invasiveness of the cells by down-regulating the expression of Akt, mTOR and their downstream effectors such as VEGF and COX-2 [57]. Pimasertib is a selective inhibitor of MEK 1/2 signalling; however, due to resistance against the drug the clinical efficacy of which has been under dispute [58]. However, in combination with dual PI3K/ mTOR inhibitor- BEZ235, it has shown to promote cell death in HCT-15 cells [59]. There are several other drugs which are shown to inhibit the colon cancer cell proliferation by modulating the PI3K/Akt/mTOR pathway; they include Indomethacin & Nimesulide [60], AZD8055 [61], NVPBEZ235 [62], BEZ235 [63], ABT-737 [64], and NVP-BEZ235 [65] (Table **2**).

Rapamycin has been a classical inhibitor of mTOR, the drug has shown to reverse the Adriamycin resistance of colon cancer cells by reducing the MDR gene expression and subsequently increasing autophagic responses [72]. Further, they also showed that a combination of these two chemotherapeutic drugs offers higher treatment efficacy when compared to their administration alone. Similarly, in HCT-116 cells, hyaluronic acid layered and dual drug-loaded (MAPK inhibitor- AZD6244 & PI3K inhibitor- PI103) chi-

Table 2. Synthetic inhibitors of PI3K/Akt/mTOR pathway in colorectal cancer.

Inhibitor	Natural or Synthetic	Nature of Study	References
Metformin	Synthetic	Preclinical- Cell lines	[52]
AZD8055	Synthetic	Preclinical- Cell lines	[61]
Diclofenac	Synthetic	Preclinical- Cell lines	[53]
Crocin	Synthetic	Preclinical- Mice model	[66]
NVPBEZ235	Synthetic	Preclinical- Cell lines	[62]
Hyaluronic acid layered chimeric nanoparticles	Synthetic nanoparticles	Preclinical- Cell lines	[67]
Tetraarsenic hexoxide	Synthetic	Preclinical- Cell lines	[55]
Catalpol	Synthetic	Preclinical- Cell lines	[56]
AZD5363+ Cetuximab	Synthetic	Patient-derived cancer cells	[68]
Inositol hexaphosphate	Synthetic	Preclinical- Cell lines	[54]
BEZ235+ Paclitaxel nanoemulsion	Synthetic	Preclinical- Cell lines	[69]
BEZ235	Synthetic	Preclinical- Cell lines	[63]
Ghrelin	Synthetic	Preclinical- Cell lines	[70]
BEZ235+ Sorafenib	Synthetic	Preclinical- Cell lines	[71]
Rapamycin	Synthetic	Preclinical- Cell lines	[72]
ABT-737	Synthetic	Preclinical- Cell lines	[64]
Tandutinib	Synthetic	Preclinical- Cell lines	[57]
Pimasertib	Synthetic	Preclinical- Cell lines	[59]
GDC-0941 + PD 0325901	Synthetic	Preclinical- Cell lines	[73]
Indomethacin & Nimesulide	Synthetic	Preclinical- Cell lines	[60]
NVP-BEZ235	Synthetic	Preclinical- Mice models	[65]

meric nanoparticles and cisplatin together inhibited the cell proliferation [67]. Supporting the combinatorial use of chemotherapeutics, studies by Zou, Li [69] showed that nanoemulsion leaded paclitaxel together with a PI3K/mTOR dual inhibitor BEZ235 showed apoptotic properties in HCT-116 and HT-29 colon cancer cells. Similarly, BEZ235 and GDC-0941 in combination with Sorafenib (a tyrosine kinase inhibitor) shown to inhibit colon cancer [71]. Further, GDC-0941 (PI3K inhibitor) and its combination with PD-0325901 (an MEK inhibitor) showed increased anticancer efficacy in a mouse xenograft model [73]. Studies by Kim, Kim [68] had further proceeded to isolate the Patient-derived colon cancer cells that are RAS wild-type and PIK3CA mutant; in such cells, a combination of cetuximab and AZD5363 considerably increased the treatment efficacy. Later, in murine models, Crocin has been shown to synergize with the activity of 5-Fu and thereby increasing the efficacy of treatment [66]. Apart from their success in the treatment of various types of cancers, the drugs also possess several negative impacts on health. The common impacts include rashes, anemia, neutropenia, thrombocytopenia, diarrhea and fatigue; minor ocular and neurological toxicities are also possible. This has led to further research in the natural inhibitors of PI3K/ Akt/ mTOR pathway; a variety of emerging molecules have shown promising effects as potent anticancer agents by interfering with this pathway.

5. NATURAL INHIBITORS OF PI3K/ Akt/ mTOR AS ANTI-COLON CANCER AGENTS

Compared to synthetic inhibitors of PI3K/Akt/mTOR signalling, natural products have gained larger attention as a PI3K-dependent drug candidate [74-77]. Since these natural products interfere with various signaling pathways at the same time, they are considered multi-targeted in action. An updated list of natural products as antineoplastic agents against colon cancer by specifically modulating PI3K signaling is summarized in (Table **3**).

Boswellic acid is a pentacyclic terpenoid compound with known anticancer potential against numerous cancers [104, 105]; in HCT-116 cells, Boswellic acid has shown to inhibit the PI3K/Akt pathway and thereby reduced the overall cell survival and promoted apoptosis [81]. The extract of *Antrodia cinnamomea*, a fungus infecting Cinnamon plants and causing Brown heart rot, has shown to induced autophagy-dependent apoptosis in colon cancer cells such as HCT116, HT29, SW480, Caco-2, and Colo205 [82]. Similarly, *Hedyotis diffusa*, a predominant component in various

Table 3. Natural inhibitors of PI3K/Akt/mTOR in colon cancer therapy.

Inhibitor	Nature of Study	Effect	References
Nobiletin	Cell lines	Sensitize cancer cells to oxaliplatin	[78]
Piperlongumine	Animal model	Inhibit DMH/DSS induced colon cancer	[79]
Cryptotanshinone	Cell lines	Inhibit invasion & migration	[80]
Boswellic acid	Cell line	Induce apoptosis & cell cycle arrest	[81]
Antrodia cinnamomea	Cell lines	Induce apoptosis in cancer cells	[82]
4- Hydroxywogonin	Cell lines	Inhibit colon cancer cell angiogenesis	[83]
Active fraction of Clove	Cell lines	Induce apoptosis in colon cancer	[84]
Hedyotis diffusa	5-Fu resistant cancer cells	Inhibit proliferation by inducing apoptosis	[85]
Wogonoside	Cell lines & mice	Induce mitochondrial-mediated autophagy-related apoptosis	[86, 87]
Coptisine	Cell lines	Activates mitochondrial associated apoptosis	[88]
Celastrol	Cell line	Inhibits cell proliferation and migration	[89]
Verbascoside	5-Fu resistant cancer cells	Sensitization of cancer cells	[90]
Resveratrol	Cell lines	Inhibits PI3K pathway and reduce proliferation	[91, 92]
Cudraflavone C	Cell lines	Induce apoptosis	[93]
Imperatorin	Cell lines	Inhibit angiogenesis and cell proliferation	[94]
Scutellaria barbata D	5-Fu resistant cancer cells	Reverse 5-Fu resistance and inhibit invasion & migration	[95, 96]
Beta Himachalenol	Cell lines	Antitumor activity	[97]
Guarana (caffeinated food item)	Cell lines	Inhibit proliferation in cancer cells	[98]
Murraya koenigii	Cell lines	Induce apoptosis in colon cancer cells	[99]
Calycosin	Cell lines	Inhibit cell proliferation	[100]
Manumycin	Cell lines	Inhibit PI3K and induce ROS mediated apoptosis	[101]
Celastrus orbiculatus	Cell lines	Ethyl acetate extract induce apoptosis	[102]
Quinazolinone chalcone derivative	Cell lines	Induce mitochondrial dependent apoptosis	[103]

traditional Chinese medicines has shown to inhibit the proliferation of 5-Fu resistant cancer cells and to induce apoptosis [85]. A glycoside of Wogonin- wogonoside, the predominant flavonoid in Scutellaria sp., has shown induce mitochondrial-mediated autophagy and apoptosis in cells and murine models [86, 87]. Another isoprenoid lipid compound from Scutellaria, β- Himachalenol, has shown to induce antitumor activity in various colon cancer cells [97]. *Murraya koenigii* or the commonly called Curry leave plant, have been known for their medicinal uses including anticancer activity. Pyranocarbazole alkaloids isolated from the *M. koenigii* have been shown to induce PI3K inhibition, G2/M arrest and apoptosis in DLD-1 cells [99]. Calycosin, an O-methylated isoflavone from the traditional Chinese medicinal plant *Radix astragali* has inhibited the proliferation of colon cancer cells such as SW480 and LoVo as well as in xenograft nude mice models in a PI3K dependent manner [100]. Apart from them, other compounds such as Manumycin [101], *Celastrus orbiculatus* ethyl acetate extract [102], Quinazolinone chalcone [103], Coptisine [88], active fraction of Clove [84], Resveratrol [91, 92], and Cudraflavone C [93] have interfered with PI3K/Akt/mTOR pathway and subsequently resulted in apoptosis and anticancer activity. Apart from these *in vitro* results, several animal models studies have shown anticancer potential. Piperlongumine, a bioactive component from long pepper, has shown a promising protective effect in Dimethyl hydrazine/ dextran sodium sulfate-induced colon cancer animal models [79].

In addition to the anticancer activity, PI3K inhibition by natural products has also been associated with reduced cancer progression events, metastasis and drug resistance [106, 107]. Reports have indicated that Nobiletin, an anticancer flavonoid isolated from Citrus peel, sensitize cancer cells to Oxaliplatin by downregulating PI3K/Akt pathway and thereby inducing apoptosis [78]. Cryptotanshinone isolated from the roots of the plant Salvia inhibited hypoxia inducing factor-1 (HIF1-alpha) and associated MMP/TIMP expression. In addition, it also downregulated PI3K signaling and thereby reduced the invasion & migration properties of colon cancer cells [80]. Similarly, Celastrol, a triterpenoid from

Celastrus plant, shown to regulate MMP3/7 expression in a PI3K/Akt dependent manner; due to the reduced synthesis of MMPs, the Celastrol treatment ultimately reduced the migration and invasiveness in colon cancer cells [89].

Plant molecules have also been important in the prevention and treatment of colon cancer angiogenesis. A flavonoid, 4- Hydroxywogonin, isolated from the Scutellaria plants has been shown to disrupt the PI3K/Akt pathway and thereby inhibit colon cancer cell proliferation and angiogenesis [83]. A furocoumarin, Imperatorin, from *Angelica dahurica*, has also shown to inhibit angiogenesis in an HIF1-alpha and mTOR dependent manner [94]. Studies have indicated that natural compounds sensitize and reverse the drug resistance in various cancer cells [108, 109]. Verbascoside [90] and extract of *Scutellaria barbata* are the two reported compounds that have shown to reverse 5-Fu resistance in colon cancer cells by disrupting the PI3K axis [95, 96]. Further extensive studies in these areas thus seem to provide more compounds capable of modulating the PI3K/ Akt/ mTOR signaling in colon cancer cells.

CONCLUSION AND AUTHORS INSIGHT ON THE TOPIC

Colon cancer is one of the predominant causes of morbidity and mortality among the world and the trend of which is keep on increasing. It has been thus an important concern for the health professionals to develop an effective strategy for the prevention of colorectal carcinogenesis and its progression. Compared to the classical cytotoxic agents the modern anticancer drugs are preferably targeting various signaling pathways that are prominent in cancers. Various interconnecting pathways are associated with the onset and progression of colon cancer, among which the most common is PI3K/Akt/mTOR pathway. This signaling is associated with the onset, metastasis, drug resistance and stemness in colon cancer cells; thus making the pathway a preferred target of drug therapeutics. Various natural and synthetic molecules have been shown to inhibit colon cancer in various preclinical and clinical models; the promising abilities of the inhibitors as clinically relevant anticancer agents.

Several synthetic drugs have shown to inhibit the proliferative properties of colon cancer cells *in vitro*; additionally, they are effective in orthotopic or xenograft mice models of colon cancer. However, the toxic effects of these synthetic inhibitors have a limiting effect on their clinical applications, which further accelerated the researches in natural product based PI3K inhibitors. Compared to the synthetic drugs, natural products have been less effective in their crude extract form, whereas purified bioactive compounds expressed similar or higher efficacies as a PI3K inhibitor. These molecules had a greater advantage of biocompatibility and reduced adverse effects. The bioactivities of these natural products are not limited to antiproliferative activity; they have been interfering with the cancer metastasis and also shown to reverse the drug resistance against various chemotherapeutic drugs such as 5-Fu. In addition, combinatorial use of the PI3K inhibitors, whether natural or synthetic, has shown to increase the treatment efficacy by reducing the concentration of the drug. However, there is no clinical information on the combinatorial uses of such PI3K inhibitors and chemotherapeutic agents. Therefore, it is necessary to evaluate the effect of a combination of these inhibitors with a standard therapeutic regimen using animal model studies and clinical trials. The review thus concludes that PI3K inhibitors are promising anticancer agents alone and in combination for future; however, the available preclinical knowledge is not sufficient to form a conclusion regarding their clinical efficacy.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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