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EVALUATION OF CHEMOPREVENTIVE RESPONSE OF PENTOXIPHYLLINE AND SILDENAFIL IN COLORECTAL CARCINOMA EXPERIMENTALLY INDUCEDIN RATS: COMPARATIVE STUDY WITH 5-FLUOROURACIL

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ABSTRACT

Objective: This study was designed to investigate some possible therapeutic mechanisms of pentoxifylline and sildenafil in the treatment of colorectal carcinoma induced by 1, 2 dimethylhydrazines in rats.

Methods: Rats were allocated into seven groups, negative control, colon cancer induced by 1,2,dimethylhydrazine, 5-fluorouracil (5-FU) (50 mg/kg)-treated, pentoxifylline (PTX) (50 mg/kg)-treated, sildenafil (0.7 mg/kg)-treated groups; the two other groups set as colon cancer induced group treated with PTX (50 mg/kg) plus 5-FU(50 mg/kg) and sildenafil (0.7 mg/kg) plus 5-FU (50 mg/kg), respectively.

Results: Biochemical results revealed significant elevation of serum carcinoembryonic antigen (CEA) levels, carbohydrate19-9 antigen (CA19-9) as colon cancer specific antigen markers; and a significant decrease in scaspase-3 (CASP3) as a marker for apoptosis, in the cancer-induced group compared to negative control group. Cancer-induced rats treated with 5-FU, with PTX or sildenafil showed a significant decrease in serum CEA and CA19-9 levels and a significant increase in CASP3 levels compared to cancer induced group. Furthermore, plasma levels of CEA and CA19-9 in 5-FU plus pentoxifylline and in 5-FUplus sildenafil groups were significantly decreased and plasma levels of CASP3 in 5-FU plus PTX, 5-FU plus sildenafil groups were significantly increased with respect to 5-FU treated group.

Conclusion: Results of the present study suggest a good therapeutic approach of the PDE inhibitors, PTX and sildenafil for intervention against progressive colon cancer with special reference to the induction of apoptosis in colon cancer cells.

Keywords: 1, 2 Dimethylhydrazines, 5-Flurouracil, Pentoxifylline, Sildenafil, Colorectal carcinoma, Carcinoembryonic antigen, carbohydrate antigen, Caspase-3.

INTRODUCTION

Colorectal carcinoma (CRC) is a major cause of cancer morbidity and mortality. Nearly 150,000 US residents diagnosed annually with CRC, and approximately one-third of CRC patients die from the disease [1]. Only about 20% of CRC cases have a familial basis; some are associated with well-defined syndromes, such as hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) [2]. However, the largest fraction of CRC cases has been linked to environmental causes rather than heritable genetic changes. Risk factors include environmental and food-borne mutagens, pathogens, and chronic intestinal inflammation that precede tumor development. The lifetime risk of CRC in the average-risk person, defined as without personal history or family history of CRC and above the age of 50, is 5%–6% [3]. Risk increases at young age (15–30%) if a first-degree relative has a history of CRC, and in some of the well-described inheritable cancer syndromes (e. g. HNPCC, FAP) to very high degree (>80%) [4].

Improvements in anticancer treatment and screening efforts that lead to early detection and removal of polyps lead to decrease in the incidence and mortality rate of CRC. The widely used chemotherapeutic agents for the treatment of CRC include 5-fluorouracil (5-FU) in combination with folinic acid (FA) and oxaliplatin [5]. It was reported that the combination of chemotherapy increase response rates (35%–53%) and prolonged progression-free survival (5–8 mo) and overall survival (14–18 mo) [6, 7]. In addition, agents targeting the vascular endothelial growth factor (VEGF) (e. g. bevacizumab) or epidermal growth factor receptor (EGFR) (e. g. cetuximab) pathways increase the efficacy of cytotoxic chemotherapy that cause increase in the survival and have led to newer method that are now the first line therapy used for the treatment of metastatic CRC [8].

Despite current therapies, 40% to 50% of CRC patients who undergo curative surgery ultimately relapse and die of metastatic disease [9].

CRC remains a genetic disease made the understanding of the underlying molecular mechanisms of CRC are the main pathway for prevention, prediction and prognosis.

Phosphodiesterases (PDEs) enzymes are responsible for the breakdown of the intracellular second messenger's cyclic guanosine monophosphate (cGMP) and cyclic adenine monophosphate (cAMP) by catalyzing the hydrolysis of the 3'-5' phosphodiester bond, result in the production of the inactive 5' nucleotides [10]. All mammalian PDEs have a catalytic site with a segment of 250-300 amino acids in the carboxyl-terminal portion of the protein (20-45% homology between gene families, 70-80% homology within gene families)[11]. Different gene families could be differentiated according to specific property, such as sensitivity to specific inhibitors, substrate affinities, biophysical and biochemical properties, and mechanisms of regulation.

Increased PDE5 expression occurs in various carcinomas, including metastatic breast, urinary bladder, and non-small cell lung cancers [12-14]. Developments of human oral squamous cell carcinoma (OSCC) result from increased PDE5 expression [15]. An increase in the level of cGMP-PDEs has been approved in various cell lines arises from bladder cancer (HTB-76, HT1376), breast cancer (MCF-7, HTB-26, and MDA-MB-468), colonic adenocarcinomas (HT29, HCT-116, SW480, and T84) and some chronic lymphocytic leukemia cells (CLL) [16]. These findings suggest that PDE5 may have a role in carcinoma, and the antineoplastic action may result from inhibiting the activity of such enzyme. Evaluation, the anticancer effect of sildenafil and other PDE5 inhibitors, carried out in multiple carcinomas and cancer cell lines. For example, vardenafil and sildenafil each may terminate tumor cell growth and induce caspase-dependent apoptosis of B-cell in (CLL) cells *in vitro* [17]. Exisulind, the non-specific PDE5 inhibitor, selectively induce the apoptosis of various breast cancer, human prostate, and colon cells. Furthermore, the effects of exisulind were not mediated through their increase in prostaglandin levels, p53, cell cycle arrest, or cyclooxygenase

inducing actions [18]. Therefore, in light of the potential involvement of these enzymes in tumorigenesis, the effects of various PDEs need to be evaluated *in vivo.*

Pentoxifylline (PTX) was reported to increase blood flow by decreasing fibroblast proliferation, inhibiting platelet aggregation, decreasing plasma fibrinogen concentrations and increasing erythrocyte deformability [19]. Its primary mechanism of action is believed to be non-specific inhibition of phosphodiesterases (PDEs), leading to accumulation of cyclic adenosine monophosphate (cAMP) which, in erythrocytes, increases deformability, and in platelets, inhibits aggregation [20]. The suggested dose of PTX is 400 mg, taken orally, three to four times a day (or 1,200 mg to 1,600 mg per day), a therapeutic dose for intermittent claudication. PTXs utility as a palliative therapy in the cancer patient and may have a promising effect in relieving some of the toxicities associated with various radio and chemotherapies including cachexia, retinopathy, myelopathy, oral and intestinal mucositis, pulmonary fibrosis, and proctitis/enteritis/mastitis [21]. The palliative dose of PTX in cancer treatment is similar to the recommended dose for the intermittent claudication and it is equally well tolerated. It believed that PTXs hemorheological effects play a significant role in its palliative utility, in addition to attenuating TNF-α; though specific mechanisms are mostly unknown [22].

Sildenafil was an oral phosphodiesterase inhibitor specific to isoform type 5 (PDE5) with selectivity for cyclic guanosine monophosphate (cGMP) [23, 24]. Nitric oxide (NO) stimulates the enzyme guanylate cyclase (GC) to convert guanosine triphosphate (GTP) to cGMP, with high levels of cGMP being responsible for the relaxation of smooth muscle [25]. Thus, sildenafil enhances the actions of the endogenous NO-cGMP pathway, by mediating the elevation of cGMP levels due to inhibiting its degradation by PDE5 [26, 27]. Due to the localization of PDE5 in the corpus cavernosum, sildenafil was successfully used in the treatment of erectile dysfunction, and pulmonary arterial hypertension where it relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure [28].

Carcinoembryonic antigen (CEA) is a complex, highly glycosylated glycoprotein belonging to the immunoglobulin superfamily and it is highly expressed during fetal development. In adult tissues, CEA is more limited in its expression but is present in epithelial and goblet cells in the colon, mucous neck cells, pyloric mucous cells in the stomach, squamous epithelial cells of the tongue, esophagus and cervix, secretory epithelial cells in sweat glands and epithelial cells of the prostate. Such antigen is typically located on the apical side of cells in the colon; however, malignant colon cancer cells may have no basal lamina and no polarity and CEA, therefore, distributed around the cell surface. It believed that this contributes to the increased levels of CEA found in the serum of cancer patients [29].

Carbohydrate antigen 19-9 (CA 19-9) is a glycolipid, which primarily synthesized by normal human pancreatic and biliary ductular cells. In addition, CA 19-9 can synthesize by gastric, colonic, endometrial and salivary epithelia [30, 31]. Like many of the other tumor markers examined, it hypothesized, that CA 19-9 may play a role in cell adhesion. This is based on the function of CA 19-9 as a ligand for the adhesion molecule E-selectin [32]. CA 19-9 used together with CEA for both diagnosis and follow-up of colorectal and gastrointestinal cancers in which the majority of colorectal carcinoma cells produce and release CEA and CA19-9 into systemic circulation. In clinical practice, those both CEA & CA19-9 remain the most frequently used tumor markers for colorectal cancer [33, 34]. CA 19-9 monitoring has been recommended for early detection of tumor recurrence after its surgical resection [34].

Cyclic guanosine monophosphate (cGMP) signaling was emerging as important intracellular signaling molecules in cancer treatment. It observed that PKG expression was lower in many tumors compared to the normal one. It also been demonstrated that apoptosis and growth inhibition were mediated by the activation of PKG, in addition to the inhibitor of cancer cell migration in human cancer cells [35]. These findings are very clinically pertinent because they confirm a role for PKG in cancer and provide a novel target for therapy. Thus, the aim of the current study was to elucidate the possible anti-tumorigenic properties of the two PDE inhibitors,

pentoxifylline and sildenafil against colorectal cancer by using experimentally rats induced with colorectal carcinoma.

MATERIALS AND METHODS

Reagents

Standard assay rat's kits (CEA, CA19-9 and CASP3) were obtained from Elabscience Biotechnology, (USA)**.**

Drugs and chemicals: 1,2 Dimethylhydrazines was obtained from Tokyo Chemical industry (TCA) chemicals, (Japan); 5-fluorouracil from Flakon, Turkey; pentoxifylline from Sukhtain Pharmaceutical product, (Jordan) and sildenafil from Drug Industries and Medical Appliances (SDI), Samarra/Iraq.

Animals

Forty-nine white Albino rats of both sexes, weighing 150-200 gm were utilized in this study; they were obtained from and maintained in the Animal House of the Pharmacy College, the University of Baghdad under conditions of controlled temperature. The animals were fed commercial pellets and tap water *ad libitum*. The study was approved by the Scientific and the Ethical Committees of the College of Pharmacy, University of Baghdad.

Induction of colon cancer by 1, 2 Dimethyl hydrazine (DMH) dihydrochloride

After the acclimatization period and for induction of colon cancer, rats (n = 42) received a dosage of 30 mg/kg body weight DMH (dissolved freshly in 0.9 % NaCl solution) subcutaneously (Sc) once in a week for 12 w. Healthy control rats (n=7) were given intraperitoneal (IP) dose of saline alone [36].

Experimental protocol

The animals used in this study were allocated into seven groups as follow:

Group I: Seven rats received IP dose of normal saline and this group served as a negative control.

Group II: Seven rats received Sc dose of DMH for 12 w. This group served as positive control of colorectal carcinoma.

Group III: Seven rats treated with IP dose of five-fluorouracil (5-FU) (50 mg/kg) daily for fourteen days after induction of colorectal carcinoma with DMH [37].

Group IV: Seven rats treated with IP dose of PTX (50 mg/kg) daily for fourteen days after induction of colorectal carcinoma with DMH. This dose has been shown to be sufficient to elicit an increase in the relative perfusion of subcutaneous redundancy improvement factor-1 (RIF-I) tumors [38].

Group V: Seven rats treated with IP dose of sildenafil (0.7 mg/kg) daily for fourteen days after induction of colorectal carcinoma with DMH [39].

*Group V*I: Seven rats treated with IP dose of sildenafil (0.7 mg/kg) plus 5-FU (50 mg/kg) daily for fourteen days after induction of colorectal carcinoma with DMH.

*Group V*II: Seven rats treated with intraperitoneal doses of PTX (50 mg/kg) plus 5-FU (50 mg/kg) daily for fourteen days after induction of colorectal carcinoma with DMH.

At the end of the experimental period (14 w), all the animals were sacrificed after euthanization with diethyl ether anesthesia 24 h later, blood sample were collected from each rat withdrawn from carotid artery at the neck into labeled centrifuging tubes and allowed to clot for 20 min at room temperature.

Biochemical analysis

The serum was separated by centrifugation at 3000 rpm for 20 min for assessments of biochemical parameters: rat carcinoembryonic antigen (CEA), rat carbohydrate antigen 19-9 (CA19-9) and rat caspase-3 (CASP3) antigen. The blood samples were immediately collected from the carotid artery.

Statistical analysis

Data were expressed as mean± standard deviation (SD) of samples. The statistical significance of the differences among various groups was determined by one-way analysis of variance (ANOVA). Differences were considered statistically significant for *p*-value<0.05.

RESULTS

Serum levels of CEA in 5-FU (50 mg/kg), PTX (50 mg/kg), sildenafil (0.7 mg/kg), 5-FU (50 mg/kg) plus PTX(50 mg/kg) and 5-FU(50 mg/kg) plus sildenafil (0.7 mg/kg) groups were significantly decreased compared with the positive control group (1.453±0.2843, 1.587±0.4890, 1.584±0.7187, 0.6186±0.3291 and 0.6543±0.3720 vs 2.519±0.5207ng/ml), respectively (table 1). Furthermore, serum levels of CEA in 5-FU (50 mg/kg) plus PTX (50 mg/kg) and 5-FU (50 mg/kg) plus sildenafil (0.7 mg/kg) groups were significantly decreased with respect to 5-FU (50 mg/kg)-treated group (0.6186±0.3291 and 0.6543±0.3720 vs 1.453±0.2843ng/ml), (table 1).

Table 1 also showed that, in colorectal carcinoma induced rats (positive control) there was significantly increased (*P<0.05*) in serum levels of carbohydrate antigen 19-9 (CA19-9) compared with the negative control groups, the levels being (10.21±3.747 vs1.104±0.4289KU/l).

Serum levels of CA19-9 in 5-FU(50 mg/kg)-, PTX(50 mg/kg)-, sildenafil (0.7 mg/kg)-, 5-FU(50 mg/kg) plus PTX(50 mg/kg)-and 5-FU(50 mg/kg) plus sildenafil (0.7 mg/kg)-treatedgroups were significantly decreased compared with the positive control group (5.486±1.235, 7.171±1.518, 6.443±2.700, 3.086±1.745 and 1.800±0.8327 vs 10.21±3.747KU/l), respectively.

Furthermore, serum levels of CA19-9 in 5-FU (50 mg/kg) plus PTX (50 mg/kg)-and 5-FU (50 mg/kg) plus sildenafil (0.7 mg/kg)-treated groups were significantly decreased with respect to 5-FU (50 mg/kg)-treated group (3.086±1.282 and1.800±0.8327 vs 5.486±1.235KU/l).

Regarding Caspase-3 (CASP3), table 1 illustrated that in colorectal carcinoma induced rats (positive control) there was a significant decrease in the serum levels of caspase-3 (CASP3) (*P<0.05*) compared with the negative control group (1.429±0.3861 vs4.129±1.050KU/l).

Serum levels of CASP3 in 5-FU (50 mg/kg) plus PTX (50 mg/kg) and 5-flurouracil (50 mg/kg) plus sildenafil (0.7 mg/kg) groups were significantly increased compared with the positive control group (5.129±1.720 and 5.057±0.3720 vs 1.429±0.3861KU/l), respectively.

Furthermore, serum levels of CASP3 in 5-FU (50 mg/kg) plus PTX (50 mg/kg) and 5-FU(50 mg/kg) plus sildenafil (0.7 mg/kg) groups were significantly increased with respect to 5-FU (50 mg/kg) treated group (5.129±1.720 and 5.057±1.652 vs 1.429±0.3861KU/l).

Table 1: Effects of treatment on carcinoembryonic antigen, Carbohydrate antigen 19-9 and Caspase-3 (CASP3) levels in rats' groups

Groups of rats N=7/each group	CEA levels (ng/ml)	CA 19-9 levels (KU/l)	CASP3 levels (KU/l)
Negative-Control (normal saline)	0.8414±0.2905	1.104±0.4289	4.129±1.050
Positive-Control (1, 2 dimethyl hydrazine)	2.519±0.5207*	10.93±2.079 *	1.429±0.3861 *
5-Flurouracil-treated (50 mg/kg)	1.453±0.2843 a	5.486±1.235 *a	2.429±1.334
Pentoxifylline-treated (50 mg/kg)	1.587±0.4890 a	7.171±1.518 *a	3.286±1.698
Sildenafil-treated (0.7 mg/kg)	1.584±0.7187a	6.443±6.754 *a	2.557±1.708
Pentoxifylline (50 mg/kg) plus 5-Flurouracil (50 mg/kg)	0.6186±0.3291 ab	3.086±1.282 ab	5.129±1.720 ab
Sildenafil (0.7 mg/kg) plus 5-Flurouracil (50 mg/kg)	0.6543±0.3720 ab	1.800±0.8327 ab	5.057±1.652 ab

Each value represents mean±standard deviation (SD). CEA: Carcinoembryonic Antigen, CA 19-9: Carbohydrate Antigen 19-9, CASP3: Caspase-3,*: Significantly different (*P*<0.05) with respect to the negative control group, a= significant difference with respect to the positive control treated group, b= significant difference with respect to the 5-FU treated group, N = number of animals.

DISCUSSION

Acting as second messengers between an extracellular signal and its elicited intracellular response, the cyclic nucleotides, cAMP and cGMP, serve as important signal transduction molecules which in turn may regulating a number of physiological processes [40]. Both the nucleotide signaling has been shown to have negative effects on cell growth and survival, depending on the cell type, extracellular environment, stimulus, and subcellular localization [41, 42]. In contrast, it has been shown that dysregulation of cyclic nucleotide signaling has been reported in various malignancies suggesting that alteration of these pathways may play an important role in tumorigenesis [43, 44].

In the current study, a preliminary trial was carried out to examine the ability of cGMP and cAMP whether or not to serve as a growth inhibitory signal in human colon cancer cells and that selective inhibition of PDE could serve as a mechanism for chemoprevention by selectively activating proapoptotic cGMP and cAMP signaling in tumor cells. After induction of colorectal carcinoma with DMH, sildenafil at a dose of 0.7 mg/kg and PTX at a dose of 50 mg/kg by i. p. doses for 14 d did produce significant changes in the cancer biomarkers serum levels (CEA and CA19-9) compared with the positive control group, and these changes were represented by a significant reduction in CEA and CA19-9 levels in pentoxifylline and sildenafil groups as compared with the positive control group (table 1).

Cancer biomarkers have become an important tool in the treatment of cancer patients, particularly in the monitoring of patients during and post treatment. Oncofetal antigens, also occasionally referred to as carcino fetal antigens, are markers that are expressed both during malignancy and neonatal development, but tend to be absent or present in low concentrations in normal adult tissues. This link between cancer and early development is not surprising, as many of the processes that contribute to cancer progression are also crucial to early development, namely, cell proliferation and cell differentiation [45]. Carcinoembryonic antigen (CEA) describes a set of highly related glycoproteins involved in cell adhesion. It is normally produced in GI tissue during fetal development, but the production stops before birth. Therefore, CEA is usually present only at very low levels in the blood of healthy adults. However, the serum levels may be raised in some types of cancer which means that it can be used as a tumor marker in clinical tests. CEA are glycosyl phosphatidyl inositol (GPI) cell surface anchored glycoproteins whose specialized sialon fucosylated glycoforms serve as functional colon carcinoma L-selectin and E-selectin ligands, which may be critical to the metastatic dissemination of colon carcinoma cells [46-48]; where, CA19-9 is considered as a ligand for the adhesion molecule E-selectin [33]. Results of this study confirmed that sildenafil-treated group at a dose of 0.7 mg/kg and pentoxifylline at a dose 50 mg/kg produced a significant reduction in CA19-9 serum levels compared with the positive control group (table 1).

In the present study, treatment with PTX (50 mg/kg) or with sildenafil (0.7 mg/kg) did not show significant changes in the CASP3 serum levels compared with the positive control group, this may attribute to the larger dose required or longer period of treatment time (table 1).

Cancer cells are in unregulated proliferation status and usually lose the ability of apoptosis due to certain signaling defects among the apoptotic pathway. However, in many cancer cells the apoptotic machinery is still intact with the potential for leading cells to death upon the induction by some exogenous factors. Therefore, one of the most common goals of cancer chemotherapy is to induce apoptosis in cancer cells while leaving non-transformed cells unharmed [49, 50].

The induction of apoptosis by the PDE5 inhibitors was demonstrated to be a complicated process. For example, cGMP-activated c-Jun NH2-terminal kinase (JNK), inhibited extracellular signal-regulated kinases 1/2 (ERK1/2) and regulated p42/p44 mitogen-activated protein kinase (MAPK) and p21. [51-54].

Pentoxifylline and sildenafil may increase the effect of 5-FU activity by blocking the substrate efflux activity [P-glycoprotein (P-gp)] of multidrug-resistant transporters which considered as a major problem in cancer chemotherapy [55, 56]. PTX treatment caused significant Pgp down-regulation in these cells via a decrease in the transcription of *mdr1* [57, 58].

Furthermore, it has been suggested that a dose-dependent increase in the percentage of apoptotic cells after PTX treatment could be mediated by pathways that include cytochrome *c* release, caspase-3 activation and poly ADP ribose polymerase (PARP) cleavage which was also documented in cutaneous T-cell lymphoma (HuT-78) [59]. These results suggested that the effect that PTX exerts on cells is at least partially through PTX promotion of apoptosis. Besides, it has been demonstrated that PTX had the ability to improve the sensitivity of several neoplastic cells to a large group of drugs that includes both substrates and non-substrates of P-gp [60-62].

Additionally, increasing of cGMP levels via their inhibition of PDE5 activity, in which the multidrug resistant transporters (ABCC4-and ABCC5) mediated efflux of cGMP, thereby increasing the likelihood of cGMP-induced activation of protein kinase G (PKG), which may produce growth suppression or apoptosis. In addition, PDE5 inhibition also leads to apoptosis through increased phosphorylation of β-catenin and/or MAP kinase/ERK kinase (MEKK1)/stress-activated protein kinase/extracellular signal-regulated kinase kinase (SEK1)/c-Jun N-terminal kinase 1 (JNK1) signaling pathways by increased PKG activation through cGMP induction. As shown that in a rat brain tumor model, the PDE5 inhibitors sildenafil and vardenafil increased the transport of doxorubicin across blood-brain tumor barrier and enhanced the efficacy of chemotherapy [63].

Tumor cells are also exposed to acute hypoxia caused by the collapse of vessels by high interstitial pressure and plugging by blood cells [64]. PTX is a unique agent known to reduce blood viscosity by increasing the deformability of erythrocytes and preventing their cluster formation, and by inhibiting platelet aggregation, thereby improving tumour microcirculation [65]. The intended drug was found to decrease elevated tumor interstitial fluid pressure (TIFP) as well as increase pO_2 in murine fibrosarcoma tumors, indicative of increased tumor perfusion [66]. These findings demonstrated a significant ability of PTX in increasing oxygenation, systemic drug delivery, and ameliorating hypoxia in solid tumors.

The apoptotic activity of PDE inhibitors was increased when combined with chemotherapeutic drug and this was previously proved by several studies that showed that the apoptotic activity of exisulind to be beneficial when combined with docetaxel in non-small cell lung cancer orthotopic lung tumor model [14] or in combination with capecitabine in Phase I and II metastatic breast cancer [12]. In a rat brain tumor model, the PDE5 inhibitors sildenafil and vardenafil increased the transport of doxorubicin across blood-brain tumor barrier and enhanced the efficacy of chemotherapy [67].

Sildenafil produced penile vasodilation and reduced tumor hypoxia in squamous carcinoma of the penis, when it was used as radiosensitizers [68]. PDE5 inhibitor's radio-sensitization mechanism may be due to increased perfusion of blood in the penile structure, leading to cGMP-induced relaxation in the corpus cavernosum, which reduces hypoxia and thus increase radiosensitivity.

Pentoxifylline can prevent the phosphorylation of serines 32 and 36 of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IκB), which sequesters NF-κB in the cytoplasm and prevents activation of target genes [69,70]. The nuclear factor-kappa B (NF-κB) transcription factor plays an important role in tumor cell growth, proliferation, invasion, and survival. In this respect, NF-κB can activate antiapoptotic genes such as Bcl-2, Bcl-XL, and survivin, affecting chemotherapy efficiency, even if the chemotherapy itself or the radiotherapy itself can activate the NF-κB factor [71], and it was found that PTX in combination with antitumor drugs such as adriamycin and cisplatin-induced in vitro and in vivo a significant increment of apoptosis in fresh leukemic human cells [72], murine lymphoma models [73], and cervical cancer cells [74]. Similar results have also been observed with PTX in other studies [59].

CONCLUSION

According to the results obtained from this study it could be concluded that, this study broaden the current understanding of the involvement of cGMP and cAMP-degrading PDE isozymes inhibitors, PTX and sildenafil, in colon tumorigenesis in which PDE had been demonstrated to be crucial for colon tumor cell growth and survival. We believed that safer and more efficacious agents for colorectal cancer can be developed through targeting PDE, which could have the potential to make a significant impact on the prevention and treatment of this malignant disease for which there is a great unmet medical need in which the treatment effects mainly depended on the induction of apoptosis in cancer cells.

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CONFLICT OF INTERESTS

Declared None

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