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REVIEW ARTICLE

Targeting of oncogenic signaling pathways by berberine for treatment of colorectal cancer

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Abstract

Studies indicate that inhibiting a single signaling pathway or one single product of a gene is insufficient for the prevention and treatment of cancer. This is due to the fact that dysregulation must occur in more than 500 genes in order to produce a cancerous phenotype. Despite this evidence, available drugs used for cancer treatment focus on a single target. Meanwhile, berberine as a nutraceutical is capable of targeting various processes involved in tumor development including proliferation, invasion, angiogenesis, and metastasis. In comparison with synthetic agents, berberine is cheaper, safer, and more available. Berberine has shown anti-inflammatory properties which make it an ideal option in order to prevent inflammation-associated cancers. Colorectal cancer is one of the most common cancers all over the world and its incidence is increasing each day. Therefore, further investigations about berberine could be helpful in the discovery of novel agents for preventing and/or treating colorectal cancer. This review emphasizes the studies investigating the roles of berberine in colorectal cancer such as controlling cell signaling pathways, inducing apoptosis, regulating microRNAs, attenuating oxidative stress, and affecting inflammation.

Keywords Berberine · Apoptosis · microRNA · Signaling pathway · Inflammation · Oxidative stress

Abbreviations

CRC	Colorectal cancer
miRNA	MicroRNA
NF-κB	Nuclear factor-κB
IBD	Inflammatory bowel disease
IMCE	Immorto-min colonic epithelial
AIF	Apoptosis-inducing factor
ROS	Reactive oxygen species
PARP	Poly (ADP-ribose) polymerase
lncRNAs	Long non-coding RNAs
CASC2	Cancer susceptibility candidate 2

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Introduction

Colorectal cancer (CRC) is the fourth cause of cancer-related death and the third most common cancer all over the world [1]. Moreover, the incidence rate of this cancer is increasing [1]. While colon and rectum are two parts of the gastrointestinal system where the CRC occurs, in most of the cases, this cancer involves the sigmoid colon [2, 3]. Adenomatous polyps or adenomas slowly lead to a large number of CRCs [4]. Due to the high rate of intestinal epithelium turnover, it is a potential hotspot for the formation of malignancies such as CRC [5]. At first, it was believed that genetic factors are responsible for morphological tissue alterations but nowadays, many investigations have shown that this disease can

also be acquired [6]. 90–95% of all cancers are attributed to lifestyle and environment [7]. Meanwhile, genetic factors are only responsible for 5–10% of cancers [7]. Evidence suggests that a higher intake of fruits and vegetables lead to a reduced risk of various cancers including esophageal cancer, gastric cancer, and CRC [8, 9]. Data have shown that approximately 35% of cancer-related deaths are associated with diet [7]. In addition, it is estimated that a remarkable number of new cancer cases are associated with suboptimal diet [10]. A large number of studies concerned with the role of diet and food consumption in cancers of the lung [11], breast [12], prostate [13], skin [14], and gastrointestinal tract [15].

Since interruption in the regulation of more than 500 genes is needed to cause a cancerous phenotype in cell signaling pathways, inhibiting one of these signaling pathways or a single gene product would neither prevent nor treat cancers [16]. In spite of this fact, most of the drugs which are currently used to treat cancers focus on a single target [16]. Thus, nowadays, a combination of multiple drugs having one target or design drugs modulating several targets is the paradigm for anti-cancer therapies [16]. Nutraceuticals which are plant-derived dietary agents have been shown to have multi-targeting features [16]. In comparison with synthetic agents, nutraceuticals are cheaper, safer and more readily available [16]. Any substance which is a food or part of food with medical and health benefits can be considered as a nutraceutical [17]. There are various nutraceuticals targeting multiple steps in the development of tumor cells [18]. Some of these nutraceuticals are allicin, apigenin, berberine, celastrol, curcumin and quercetin [19]. These agents are involved in different cancer mechanisms including survival, proliferation, invasion, angiogenesis, and metastasis [19, 20]. In addition, nutraceuticals modulate nuclear factor-κB (NF-κB) which is an important inflammatory transcription factor [19]. Therefore, nutraceuticals affect inflammation which is a prominent agent for enhancing the progression of tumors [19]. We further discuss the role of berberine as a nutraceutical and its anti-tumor effects on CRC molecular aspects and cell signaling pathways.

Colorectal cancer risk and preventive factors

Based on a study on twins, inheritable factors can cause about 35% of CRC risk [21]. Genetic factors playing a role in this cancer are not well-understood yet except for the hereditary types like familial adenomatous polyposis and hereditary non-polyposis colon cancer (Lynch syndrome) [21]. Moreover, a small association between single nucleotide polymorphisms (SNPs) and CRC risk is suggested by meta-analyses studies [21]. Findings suggest that overall incidence is higher in men compared to women [22]. Age and gender, two important factors involved in CRC, are accompanied by risk factors such as inflammatory bowel disease (IBD) [23], obesity [24], diabetes [25], smoking [26], immoderate consumption of alcohol [27], red and processed meat consumption [28] and family history of CRC [29]. Frequently, these factors happen at the same time and interact with one another. The role of infectious agents like Helicobacter pylori has been investigated in some novel studies [30]. There are several ways to prevent this cancer including hormone replacement therapy [31], aspirin [32], physical activity [33] and removing precancerous lesions with the help of endoscopy [34, 35]. Furthermore, evidence has shown that consumption of certain foods can prevent CRC including fish [36], dairy products [37], whole grains [38], fruit, vegetables and cereal fiber [39].

Berberine effects on different health conditions

An ammonium salt from the protoberberine group of isoquinoline alkaloids called berberine has vast pharmacological effects such as antimicrobial, antidiabetic and anti-tumor functions [40, 41]. Several plants have been found to have berberine including Berberis (e.g. Berberis aquifolium, Berberis vulgaris, Berberis aristata), Hydrastis canadensis, Xanthorhiza simplicissima, Phellodendron amurense, Coptis chinensis, Tinospora cordifolia, Argemone mexicana, and Eschscholzia californica [40]. Berberine has shown anti-inflammatory and antioxidant properties in vitro [42]. It has demonstrated protective characteristics such as neuroprotective and cardiovascular protective within animal models [43, 44]. Moreover, numerous studies present that berberine decreases lipid levels and improves resistance to insulin in humans [40]. In this review, we focus on multiple roles of berberine in CRC tumor development such as inducing programmed cell death (both caspase-dependent and caspase-independent), regulating microRNAs (miRNAs), controlling signaling pathways (Pin1/beta-catenin/cyclinD1 pathway, Wnt/β-catenin pathway, COX-2/PGE2- JAK2/STAT3 pathway and IL-6/STAT3/NF-κB pathway), and acting as an anti-inflammatory and antioxidant agent.

Berberine-induced cell death in CRC

One of the well-known types of programmed cell death is apoptosis which happens in a caspase-dependent manner [45]. There are two pathways regulating caspase-dependent apoptosis, extrinsic and intrinsic [45]. The former one is “death-receptor-mediated” and the latter one is “mitochondrial-mediated” [45]. An alternative mitochondrial route which is caspase-independent is another way that programmed cell death can occur [46]. What leads to

this process is the loss of mitochondrial function causing caspase-independent cell death by the release of mitochondrial proteins [47]. Berberine has been observed to induce apoptosis in colon cancer cells with many different mechanisms. One of these mechanisms is through the caspase 3 and caspase 8 activation as well as cleavage of poly ADP-ribose polymerase (PARP) [48]. Meanwhile, it remarkably reduces c-IAP1, Bcl-2, and Bcl-(XL) expressions which are anti-apoptotic factors [48]. Berberine-induced apoptosis leads to JNK and P38 MAPK phosphorylation and formation of reactive oxygen species (ROS) [48]. Besides, activation of JNK and p38 signaling modulators in berberine-induced apoptosis causes an increase in phospho-c-Jun, FasL, and t-BID cellular levels [48].

Berberine activates a metabolic regulator called AMP-activated protein kinase (AMPK), [49]. Mammalian target of rapamycin (mTOR), a downstream target of AMPK, is suppressed by berberine [49]. In vitro, berberine leads to a reduction in cyclin D1 and survivin expression, NF-κB activity inhibition, an increase in caspase 3 cleavage and induction of p53 phosphorylation [49]. Also, berberine results in AMPK activation, mTOR suppression, p65 phosphorylation and caspase 3 cleavage activation in vivo [49]. In Dai et al. [50] study, it is observed that when treating cells with berberine, lncRNA cancer susceptibility candidate 2 (CASC2) was up-regulated. Silencing the lncRNA CASC2 led to the suppression of apoptosis which was induced by berberine [50]. Thus, this lncRNA is a crucial element for berberine-induced apoptosis. LncRNA CASC2 acts as a tumor suppressor in different cancers and makes a suppressing effect on Bcl-2 protein level [50]. Since it is shown that lncRNA CASC2 regulates expression of Bcl-2 protein, but it doesn't affect its mRNA levels, it can be concluded that its regulatory effect is at the post-transcriptional level [50]. Altogether, berberine induces apoptosis mediated by lncRNA CASC2 and has anti-tumor effects such as suppressing tumor cells viability [50]. In an in vitro study on the mouse immorto-Min colonic epithelial (IMCE) cells, administering berberine induced the release of apoptosis-inducing factor (AIF), caspase-independent cell death mediator, in a manner which was dependent on ROS production [51]. Additionally, berberine stimulates the release of cathepsin B and activation of PARP which are two targets of ROS production in cells [51]. As a result, AIF activation leads to caspase-independent cell death in colon cancer tissues [51]. Since normal colon epithelial cells do not show such a vulnerability to berberine-induced cell death, this anti-proliferative feature of berberine is specific for colon tumor cells [51].

Berberine and miRNA

Based on recent evidence, miRNA changes are responsible for the formation and progression of various human cancers [52, 53]. Location of miRNA genes in cancer-related genomic regions, epigenetic processes and changes in miRNA processing machinery are some of the explanations about why these genes are differentially expressed in malignancies compared with normal tissues [54]. Due to the unique miRNA-expression features of tumors, miRNAs can be used in different ways including diagnosis, staging, progression, prognosis, and response to treatment [54]. Berberine regulatory effects on miRNAs which are dysregulated in malignancies make it a potential agent for treating cancers. Multiple myeloma [55], ovarian cancer [56], endometrial cancer [57] and CRC [58] are some examples of cancers in which berberine can affect miRNAs.

Berberine is capable of changing the expression of various genes which are involved in the apoptosis regulation, progression of cell cycle and drug resistance by the TP53 stimulation and miRNAs expression [59]. Compared to normal tissues, mi-429 has a higher expression level in CRC which implies that it is an oncomir [60]. While berberine inhibits the E-cadherin and partitioning defective 3 (Par-3), with berberine and evodiamine treatment, there is a reduction in miR-429 levels in the tumor cells [58]. Berberine and evodiamine have demonstrated a notable impact on DNMTs expression and target miRNAs during colon cancer formation [58]. Their effect on miR-29a expression was more clear which indicates that berberine and evodiamine mediate the DNMTs expression and miRNAs through a process engaging various factors targeting [61]. During the progress of CRC, expression of microRNA-296 (miR-296) is lost progressively and is associated with metastasis [62]. In NVP-AUY922 treatment, drug resistance has been observed as a side effect due to the higher expression levels of survivin [63]. Berberine decreases the growth of the normally resistant cells when it is used in combination with NVP-AUY922 which is an HSP-90 suppressor [63]. Berberine exerts this function by inhibiting Pin1/beta-catenin/cyclinD1 signaling pathway mediated by miR-296-5p and suppressing the expression of CDK4 [63]. As we mentioned above, Dai et al. [50] concluded that berberine upregulates the CASC2 which is critical for anti-tumor effects of berberine. Meanwhile, it is suggested that CASC2 plays its anti-tumor role by acting as competing endogenous RNA through miR-18a sponging in CRC [64].

Berberine role as an RXRα in cell signal pathway

One of the possible reasons for the anti-tumor characteristics of berberine is its strong binding to DNA which may result in epigenetic changes [65]. A reduction in the number and the size of colorectal polyps has been seen in patients who suffered familial adenomatous polyposis with the oral administration of berberine soon after the polypectomy [66]. This effect was associated with significant diminution in the expression of cyclin D1 [66]. Cyclin D1 up-regulation is linked with tumorigenesis of the colon and its metastasis which is due to the activation of Wnt/β-catenin signaling pathway [67]. Whereas, berberine has shown preventive effects on the β-catenin pathway [67]. Wnt/β-catenin signaling pathway has a wide interaction with members of the nuclear receptor superfamily [68]. One of these members is retinoid X receptor α (RXRα) which has been indicated modulatory roles on the β-catenin signaling [69, 70]. Therefore, the unusual activation of the β-catenin pathway could be a result of abnormal RXRα function [71]. In fact, in colon tumor tissues, abnormal alteration of RXRα protein is usually seen [72]. Moreover, RXRα genetic diversity is linked with the colorectal adenoma risk of recurrence [73]. Besides, in CRC tissues, excessive phosphorylation of RXRα occurs which is a cause to inhibition of RXRα transactivation [74]. Based on several findings investigating the role of RXRα agonists and factors binding to it, RXRα can be considered as a target for colon cancer treatments [71, 75–77]. In addition, Ruan et al. [71] found that berberine could be a novel RXRα activator. They gathered evidence suggesting that binding of berberine to RXRα by a unique binding mechanism, which enhances the interaction between RXRα and nuclear β-catenin, results in suppression of β-catenin signaling both in vitro and in vivo animals [71].

Berberine and inflammation

There is an important association between chronic inflammation and cancer progression [78]. 15–20% of all cancer-related deaths have been estimated to be related to inflammatory processes and underlying infections [79]. IBDs such as Crohn's disease and Ulcerative colitis lead to a higher risk of colitis-associated CRCs which show poor prognoses [80, 81]. These findings imply that chronic inflammation in the gut could lead to the initiation of tumorigenesis and promoting cancer development. Besides, the role of inflammatory cytokines and tumor-infiltrating immune cells has been indicated in CRC after the primary tumors development [82]. Innate immune cells (including macrophages, neutrophils, and dendritic cells) and adaptive immune cells (including T and B cells) are involved in the inflammation giving rise to the secretion of extremely genotoxic compounds, oxygen/ nitrogen reactive species [83]. In addition, immune cells result in the release of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-1β and tumor necrosis factor-α (TNF-α) and growth factors [84]. While these mediators are produced through various signaling pathways such as NF-κB, signal transducer and activator of transcription 3 (STAT3), PI3K/AKT, and cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2), they have a role in multiple mechanisms such as proliferation, angiogenesis, invasion and metastasis [84].

Due to the similarities of inflammatory environment and tumor microenvironment, it is implied that the same agents are involved in the chronic intestinal inflammation and formation of CRC [85]. Thus, there is a link between inflammatory mediators and prevalence of colorectal adenomas [85]. In a dose-dependent manner, COX-2 is inhibited by berberine at mRNA and protein level [86]. Besides, berberine reduces COX-2 activity and the concentration of prostaglandin E2 [86]. These data suggest that berberine suppresses the growth and proliferation of human colon cell line, HT29 [86]. Another finding indicates that berberine decreases JAK2 and STAT3 phosphorylation as well as MMP-2/-9 expression [87]. The reduction in the JAK2/STAT3 signaling is a consequent of attenuating the COX-2/PGE2 expression [87]. As a result, berberine prevents the proliferation, invasion, and metastasis of CRC cells both in vitro and in vivo by down-regulation of COX-2/PGE2-JAK2/STAT3 signaling pathway [87]. Li et al. [88] found that berberine exerts its anti-proliferative effect by involving inflammatory response-driven EGFR signaling in order to prevent the further progress of colitis-associated CRC. In a recent study of ulcerative colitis, it is reported that treatment with berberine hydrochloride and sulphasalazine led to the suppression of IL-1, IL-1β, IL-6, IL-12, TNF-α, TGF-β, and IFN-γ and higher expression levels of IL-4 and IL-10 [89]. Biochemical analyses suggest a higher expression level of p-STAT3 and down-regulation of p-NF-κB (p65) [89]. Consequently, the suppressing effect of berberine hydrochloride on IL-6/STAT3/NF-κB signaling pathway is the probable process by which berberine plays its anti-inflammatory role [89].

Antioxidative effects of berberine on CRC

Oxidative stress affecting DNA sequences could lead to the CRC and results in the transformation of adenoma to carcinoma [90]. Several studies suggested that antioxidants

have positive impacts on CRC [91]. Although there is not enough evidence to confirm the exact effects of antioxidants on human CRC, antioxidant consumption is recommended to the patients having a history of CRC or IBD [90]. Gegen Qinlian is a decoction of Chinese medicinal herb which is proved to have beneficial effects in the ulcerative colitis [92]. Baicalin, glabridin, and berberine are some of the active components of Gegen Qinlian which are indicated to reduce the inflammation and oxidative stress in vivo and in vitro [93–95]. Li et al. [96] investigated the effect of Gegen Qinlian on mice ulcerative colitis and concluded that this decoction decreases inflammation and oxidative stress as evidenced by a reduction in the activity of myeloperoxidase and malondialdehyde level and increase in the content of glutathione in vivo. Other findings also show that berberine decreases myeloperoxidase levels as well as increases the levels of superoxide dismutase and catalase [97]. Myeloperoxidase, superoxide dismutase, and catalase are enzymes which play important roles in inflammation and oxidative stress [98–102]. While myeloperoxidase is an indicator of oxidative damage, superoxide dismutase and catalase serve as antioxidants [103]. Cytokines, growth factors and oxidative stress are activators of STAT3 which is a transcriptional activator [104, 105]. Berberine has been shown to prevent the phosphorylation of STAT3 in mice with colitis suggesting that the anti-inflammatory and antioxidant effects of berberine in colitis are possibly related to the reduction of p-STAT3 [97].

Conclusions

Berberine is an isoquinoline alkaloid which is found in several plants such as Berberis, Xanthorhiza simplicissima, Phellodendron amurense, Coptis chinensis, and Tinospora cordifolia. Berberine has shown multiple bioactivities such as improving insulin resistance and anti-tumor properties as well as cardiovascular protective and neuroprotective features. Berberine anti-tumor characteristics encompass preventing tumor growth, invasion, migration and metastasis. Related to CRC, berberine has demonstrated many functions which may lead to prevention or treatment of this cancer. For instance, berberine induces both caspase-dependent and caspase-independent programmed cell death, regulates miRNAs, and involves different signaling pathways. Moreover, berberine attenuates oxidative stress and inhibits inflammation. In order to exert its functions, berberine makes various effects on proteins (c-IAP1, Bcl-2, and Bcl-XL), enzymes (PARP, DNMT), and miRNAs (miR-429, miR-296) (Table 1; Fig. 1). Altogether, there is a necessity for further comprehensive investigations with the purpose of clarifying berberine roles in CRC. Hopefully, berberine can be used

Table 1 Experimental studies that investigated the apoptosis-inducing role of berberine in CRC

Dosage	Treatment duration	Function	Type of cell	Study model	References
40 µM	48 h	Induces apoptosis, upregulates LncRNA CASC2	HT29	In vitro	[50]
50 µM and 100 µM	18 h	Induces caspase-independent cell death, stimulating AIF	IMCE	In vitro	[51]
50 µM	24 h	Induces caspase 3- and caspase 8-dependent cell death	SW620	In vitro	[48]
Up to 100 µmol/L	24, 48 and 72 h	Actives AMPK, increases caspase 3 cleavage	HCT116, SW480	In vivo, in vitro	[49]
10 µM	24 h	Induces apoptosis mediated by mitochondria central roll	HCT116	In vitro	[106]
120 and 240 mg/kg	Five times a week up to the 20th week	Induces caspase 3-dependent apoptosis	HCT116	In vitro	[107]
10 µM	48 h	Inhibits NF-κB activation, enhances CPT-11-induced apoptosis	HCT116	In vitro	[108]
25 µM	24 h	Induces caspase 3- and caspase 9-dependent apoptosis	SW480	In vitro	[109]
10 µM and 50 µM	4 days and 2 days, respectively	Induces apoptosis in which NAG-1 and ATF3 expression is involved, reduces cell proliferation	HCT116	In vitro	[110]
–	–	Induces apoptosis which possibly involves death receptor pathway	HCT8	In vitro	[111]
75 mg /Kg	15 days prior DMH intoxication and concurrently with DMH over eight weeks	Induces apoptosis, ameliorates 1,2 Di methyl hydrazine induced colon cancer	–	In vitro	[112]

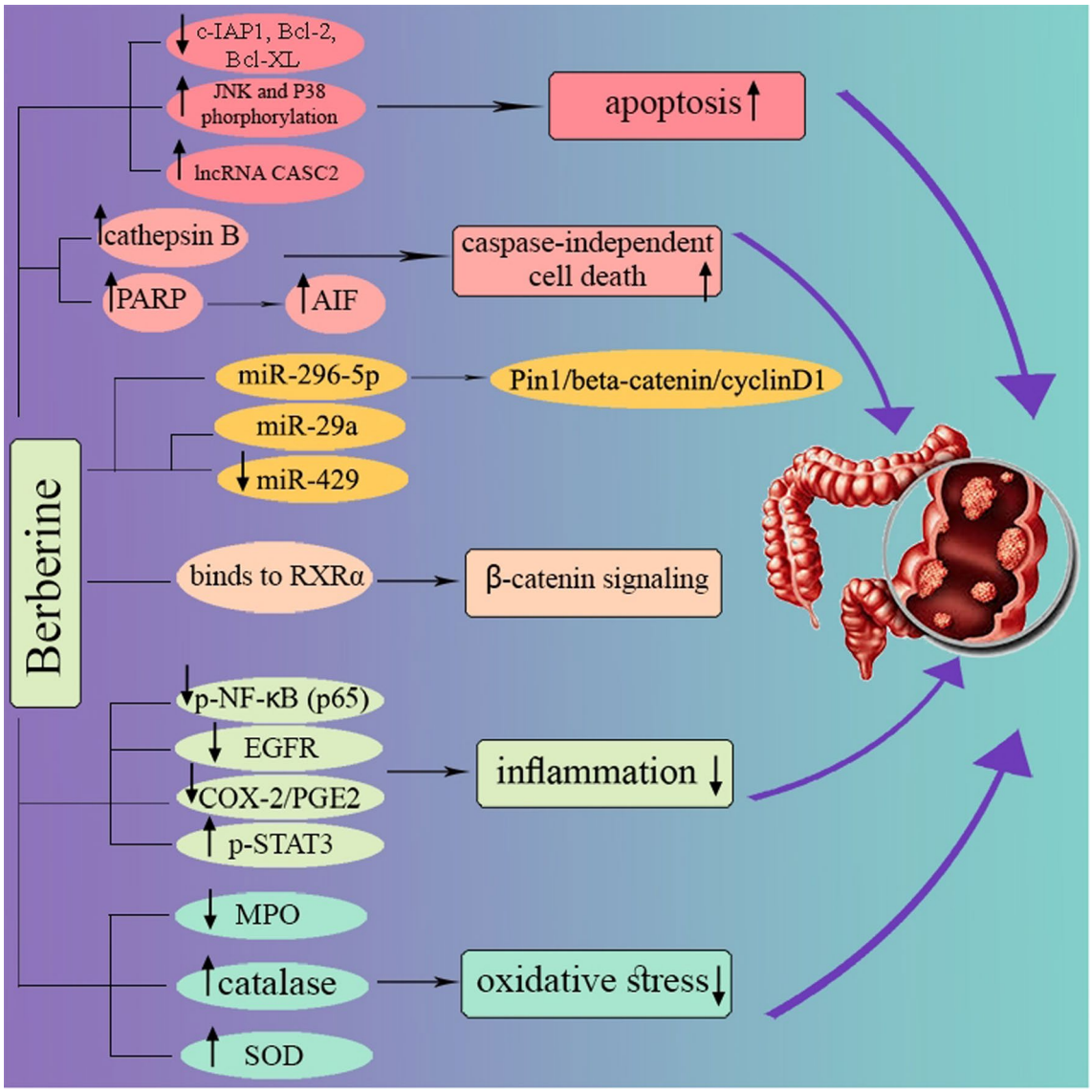

Fig. 1 Schematic representation in targeting different pathways using berberine as a novel therapeutic approach in the treatment of colorectal cancer

as a novel multi-targeting therapeutic agent instead of the current single-targeted drugs.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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