

Therapeutic Role of Morin in Colorectal Cancer: Molecular Mechanisms

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Abstract:

Colorectal cancer (CRC), the third most prevalent cancer in the world, typically originates from abnormal crypts in the intestine generated by cancer stem cells (CSCs). Subsequently, these abnormal crypts progressively evolve into polyps and eventually colorectal cancer through multiple molecular mechanisms. During carcinogenesis and progression, morin, a flavonoid with diverse pharmacological activities, exhibits remarkable anti-cancer effects. Numerous studies have confirmed that morin exerts inhibitory effects on CRC through multiple pathways, including the regulation of reactive oxygen species (ROS) levels, suppression of nuclear factor κ -B (NF- κ B) activity, induction of apoptosis, inhibition of tumor energy metabolism, and suppression of CSCs. The anti-cancer effects of morin involve several signaling pathways, such as PRKR-like endoplasmic reticulum kinase (PERK)/Nuclear factor erythroid 2-related factor 2 (Nrf2), NF- κ B, AKT, β -catenin/c-Myc, and signal transducer and activator of transcription 3 (STAT3). Furthermore, combination therapy involving morin with other anti-cancer drugs enhances sensitivity to 5-fluorouracil, thereby exerting an effect on drug-resistant colorectal cancer. This paper reviews the pharmacokinetic properties of morin, along with its anticancer effects and underlying mechanisms in CRC. Given its multi-targeted pharmacological effects, capacity to enhance the efficacy of other anti-cancer medications, and excellent safety profile, morin exhibits promising potential as a preventive and therapeutic intervention for CRC.

Keywords: Colorectal cancer; flavonoids; morin; molecular mechanisms.

1. Introduction

Cancer, as a significant public health challenge, poses a substantial impediment to increasing life expectancy globally. According to GLOBOCAN 2020 data, colorectal cancer (CRC) has become the third most prevalent cancer in the world, with an estimated 1.88 million new cases globally in 2020, the number of which is projected to rise to 2.5 million globally by 2035 [1]. Despite notable advancements in its treatment, CRC remains the second leading cause of cancer-related mortality, accounting for 920,000 reported fatalities in 2020 [1]. Consequently, it is imperative for researchers to explore novel therapeutic interventions or compounds to mitigate both the occurrence and progression rates of this disease.

In cancer therapy, flavonoids have garnered increasing attention from researchers due to their potent anti-cancer properties. Morin (2',3,4',5,7-pentahydroxyflavone) belongs to the class of flavonoids, initially discovered in the Moraceae family. The compound morin can be extracted from a variety of plants, including figs (*Ficus carica L*) and almonds (*Prunus dulcis Mill.*) [2, 3]. Extensive re-

search has been conducted on morin owing to its pharmacological properties, encompassing its antioxidative potential, anti-inflammatory activity, and anticancer effects [4-7]. Numerous studies have demonstrated that morin exerts a significant inhibitory impact on CRC by impeding its initiation and progression through multiple pathways [8-13]. Importantly, morin exhibits mild toxicity with safety confirmed by several experimental investigations [14]. Therefore, morin holds great promise as an effective anti-cancer agent for tumor prevention or adjuvant therapy.

This review comprehensively summarizes the anti-cancer mechanisms of morin, encompassing diverse facets of reactive oxygen species (ROS) regulation, nuclear factor κ -B (NF- κ B) signaling pathway modulation, apoptosis induction, tumor energy metabolism regulation, and cancer stem cells (CSCs) targeting. These mechanisms involve intricate signaling pathways, including PRKR-like endoplasmic reticulum kinase (PERK)/Nuclear factor erythroid 2-related factor 2 (Nrf2), NF- κ B, β -catenin/c-Myc, AKT, and STAT3.

2. Structural Features of Morin

In terms of chemical structure, morin belongs to the flavonoid group due to its 15-carbon-atom backbone structure comprising two benzene rings (A and B) and a heterocycle (C). Flavonoids can be classified into different structural classes based on the degree of oxidation and the position of substituent groups on the C ring. With its 3-hydroxyflavone skeleton, morin belongs to the subgroup of flavonols characterized by a γ -pyranone linking two benzene rings with five hydroxyl groups at the 2', 4', 3, 5, and 7 positions (Figure 1) [15].

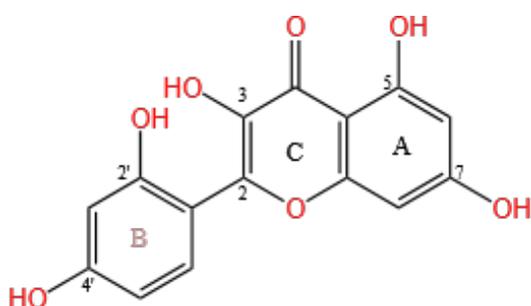


Fig. 1 Chemical structure of morin

3. Pharmacokinetic Properties of Morin

The oral absorption of morin was found to primarily occur in the colon rather than the small intestine [3, 16]. Within the colon, gut microbes convert morin into morin aglycone, which exhibits enhanced intestinal absorption [3]. In intestinal epithelial cells, morin can bind to and inhibit multidrug resistance-associated protein 1 and also non-competitively inhibit P-glycoprotein, resulting in reduced uptake of morin itself. Consequently, bioavailabil-

ity of morin is limited [3]. However, uptake may not be affected in high concentrations of morin because the binding of morin to multidrug resistance-associated protein 1 can be saturated [3]. Therefore, through inhibition of multidrug resistance-associated protein 1 and P-glycoprotein activity, morin reduces efflux and promotes the absorption of other drugs.

Upon absorption, morin undergoes metabolism in the intestine and liver by uridine diphosphate glucuronosyltransferase, sulfotransferase, and catechol-O-methyltransferase to produce glucuronide conjugates, sulfate conjugates, and methylated conjugates [3]. Notably, both morin itself and its metabolites are co-localized in plasma and urine, suggesting that both morin and its conjugated metabolites should be focused on in pharmacological studies [3].

Overall, morin exhibits significant nonlinear metabolic pharmacokinetics in healthy rats, with dose-dependent pharmacokinetic parameters that may be attributed to enhanced membrane permeability and metabolic saturation phenomena [16]. It is noteworthy that the pharmacokinetic behavior of morin might vary in different disease states due to the influence of the underlying pathophysiological processes. Therefore, future investigations are warranted to compare the pharmacokinetic behavior of morin under normal physiological conditions and in colorectal cancer.

4. Molecular Mechanisms of Morin in CRC

The remarkable anti-cancer effects of morin have been demonstrated by the regulation of ROS levels, modulation of the NF- κ B signaling pathway, induction of apoptosis, modulation of tumor energy metabolism, as well as reduction of CSCs (Figure 2).

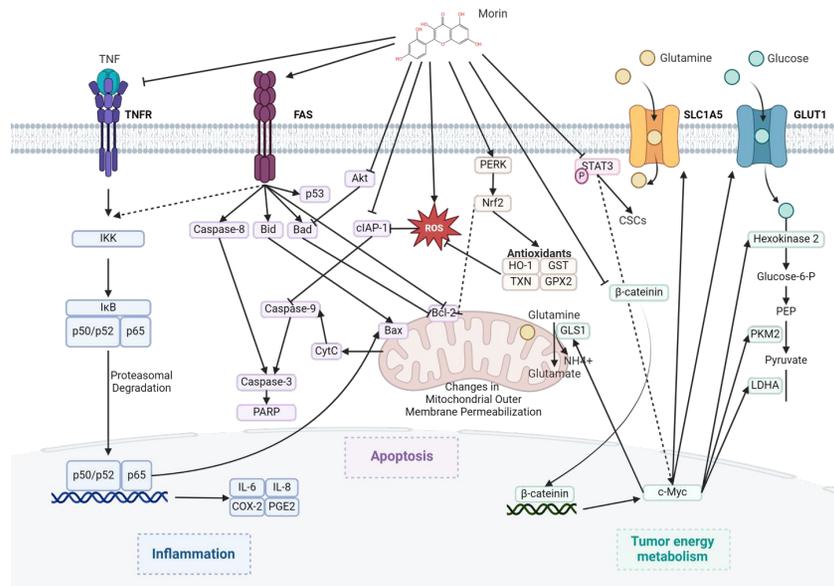


Fig. 2 Anti-cancer mechanism of morin in CRC.

By inhibiting the activation of IκB kinase, Morin effectively suppresses the NF-κB signaling pathway, resulting in a decrease of inflammatory factors and anti-apoptotic proteins. Additionally, Morin activates the PERK/Nrf2 signaling pathway to enhance antioxidant levels and alleviate oxidative stress. Morin induces apoptosis via both exogenous and endogenous pathways: it up-regulates expression of Fas receptor in the exogenous pathway while concurrently promoting ROS generation, down-regulating levels of anti-apoptotic protein, and up-regulating levels of pro-apoptotic protein in the endogenous pathway. Inhibition of NF-κB also augments apoptosis through the endogenous pathway. Morin impedes tumor energy supply by inhibiting the β-catenin/c-Myc signaling pathway, leading to downregulation of glucose and glutamine transporter levels as well as inhibition of metabolic enzyme activities. Morin suppresses CSCs by inhibiting the STAT3 signaling pathway. TNF, tumor necrosis factor; IKK, IκB kinase; IL-6, interleukin-6; IL-8, interleukin-8; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; FAS, Fas cell surface death receptor; PARP, poly ADP-ribose polymerase; Bax, BCL2-associated X protein; CytC, cytochrome c; ROS, reactive oxygen species; PERK, PRKR-like endoplasmic reticulum kinase; Nrf2, nuclearrespiratory factor 2; CSCs, cancer stem cells; SLC1A5, solute carrier family 1 member 5; GLUT1, facilitated glucose transporter member 1; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; GLS, glutaminase. Figure credit: original, created with Biorender.com.

4.1 Regulation of ROS

ROS is an inevitable byproduct of mitochondrial oxidative metabolism [17]. Among them, the hydroxyl radical

exhibits the highest oxidizing capacity and is capable of causing intracellular macromolecular damage, whereas hydrogen peroxide possesses a relatively weaker oxidizing potential but serves as an indispensable signaling molecule in diverse cellular processes [17]. ROS play both physiological roles and pose potential hazards; thus, it is crucial to maintain their normal and controllable levels for organismal homeostasis. Notably, the impact of ROS on cancer progression closely correlates with their concentration and may either promote or inhibit cancer development and progression. Under conditions of oxidative stress, ROS can modify the expression and activity of specific proteins through DNA damage, mutation induction, and other pathways, which in turn facilitate malignant cell transformation and tumorigenesis [17]. However, in cases of increased concentrations, the presence of ROS can hinder the cellular cycle and induce apoptosis or autophagy to combat cancer [17].

In Wistar rats with CRC induced by 1,2-dimethylhydrazine (DMH), prior research has shown that morin activates the PERK/Nrf2 signaling pathway to increase the expression of heme oxygenase 1, glutathione peroxidase 2, thioredoxin, glutathione S-transferase, uridine diphosphate glucuronosyltransferase, and other antioxidants. This ultimately results in a reduction in the carcinogenic potency of the carcinogen DMH and inhibition of tumor growth. Similarly, in DMH-induced Wistar rats with CRC, morin treatment increased antioxidant levels, including superoxide dismutase, glutathione S-transferase, catalase, glutathione reductase, glutathione peroxidase, and reduced glutathione. Simultaneously, it decreases tissue levels of lipid peroxidation products such as thiobarbituric acid substances,

lipid hydroperoxides, and conjugated dienes [10]. When ROS react with biological molecules like phospholipids and cholesterol esters during lipid peroxidation reactions, the fluidity and permeability of biological membranes are altered, leading to changes in cellular structure and function. Therefore, morin reduces intestinal tumor incidence and prevents intestinal tumor diversity in DMH-induced Wistar rats with CRC by mitigating oxidative damage [10]. Conversely, morin can also exert its anti-cancer effects through the generation of ROS. Cancer cells exhibit higher sensitivity to rapid increases in ROS levels compared to normal cells. It has been reported that morin induces depolarization of mitochondrial membrane potential ($\Delta\Psi_m$) by promoting ROS generation and decreasing catalase and glutathione levels in SW480 and HCT-116 colon cancer cells. This leads to the release of cytochrome C into the cytoplasm, ultimately activating the caspase-dependent endogenous apoptotic pathway [5, 6, 11].

In conclusion, morin exhibits intricate regulation of ROS levels (Table 1). On the one hand, by reducing ROS levels, morin can mitigate lipid peroxidation and thereby reduce tumorigenesis, playing a preventive role against tumors. On the other hand, by increasing ROS levels within tumor cells, morin induces apoptosis and decelerates tumor progression, thus manifesting its therapeutic effects on tumors.

4.2 NF- κ B Signaling Pathway

Numerous biological processes, encompassing inflammation, cellular proliferation, cell death, as well as cellular migration, invasion, and metastasis, rely on the NF- κ B signaling pathway [18]. The NF- κ B signaling pathway could generally be categorized into canonical and non-canonical pathways, with the former being the most studied and in-depth. NF- κ B is rendered inactive through binding with the inhibitor of NF- κ B (I κ B) to form trimers that are sequestered in the cytoplasm. The activation of the canonical pathway can be initiated by various signals, including damage-associated molecular patterns, pathogen-associated molecular patterns, and pro-inflammatory cytokines [18]. Upon activation of the canonical pathway, I κ B kinase is activated, leading to phosphorylation of I κ B and its subsequent dissociation from the trimeric complex. This allows the translocation of NF- κ B dimers into the nucleus, where NF- κ B dimers promote the transcription of NF- κ B target genes. Given its association with CRC development, progression, and resistance to chemotherapeutic agents, inhibition of NF- κ B activity holds promise as a potential therapeutic target for CRC [18].

Previous research has shown that morin possesses the ability to attenuate the occurrence of colorectal precancerous lesions and inhibit CRC cellular proliferation

and tumor growth by effectively suppressing the NF- κ B signaling pathway [7, 8]. Tumor necrosis factor (TNF) is acknowledged as a cytokine capable of inducing NF- κ B activation and apoptosis. In HCT-116 cells, morin effectively suppressed TNF-induced expression and phosphorylation of p65-NF κ B, thereby inhibiting the downstream production of interleukin-6 and interleukin-8 through the NF- κ B signaling pathway, ultimately leading to the inhibition of CRC cell proliferation [7]. In Wistar rats with CRC induced by DMH, morin effectively inhibited activation of NF- κ B by suppressing activation of I κ B kinase and preventing dissociation of I κ B, thereby down-regulating downstream pro-inflammatory factors (TNF- α , interleukin-6, cyclooxygenase-2, and the prostaglandin E2) as well as BCL2-associated X protein levels. This ultimately prevented CRC development by reducing oxidative stress levels and inducing apoptosis [8]. Overall, these results indicated that morin exerts anti-inflammatory effects while promoting apoptosis as well as preventing colorectal cancer initiation and controlling tumor progression by inhibiting the NF- κ B signaling pathway (Table 1).

4.3 Apoptosis

Apoptosis is a genetically regulated cell death by multiple genes involving both exogenous and endogenous pathways. The exogenous pathway is initiated by the binding of death ligands (e.g., Fas Ligand) to transmembrane death receptors (e.g., Fas Receptor). Conversely, the endogenous pathway primarily relies on the mitochondria-dependent apoptotic pathway mediated by the Bcl-2 family, which regulates cell death through modulation of outer mitochondrial membrane permeability [19]. When intracellular apoptotic stress signals are present, levels of pro-apoptotic proteins become elevated, thereby facilitating the expulsion of cytochrome C from the mitochondria into the cytoplasm [20]. Ultimately, activation of both exogenous and endogenous pathways leads to caspase protease family activation, thereby inducing apoptosis [19].

It has been observed that the apoptotic pathway can be induced by morin in various CRC cell lines, including COLO205, SW480, HCT-116, Ccao-2, HT-29, and SW620. The underlying mechanism may involve the inhibition of NF- κ B and AKT signaling pathways [5, 6, 11, 12]. Morin-induced apoptosis encompasses both the activation of endogenous and exogenous pathways. By upregulating the Fas receptor and activating caspase-8-dependent apoptosis, morin activates the exogenous apoptotic pathway [5]. In terms of the endogenous apoptotic pathway, morin triggers caspase-9-dependent endogenous apoptosis by regulating ROS generation as well as up-regulating the expression of p53 and pro-apoptotic proteins (BCL2-associated X protein, BH3 interacting domain

death agonist, and BCL2 associated agonist of cell death), while down-regulating the expression of anti-apoptotic proteins (BCL2 and baculoviral IAP repeat containing 2). This may lead to the loss of the $\Delta\Psi_m$ and the release of cytochrome C [6, 11, 12]. Ultimately, activated caspase-8 and caspase-9 initiate caspase-3 activation through protein hydrolysis to exert apoptotic effects. Importantly, the role of AKT as a key upstream signaling molecule in morin-induced apoptosis has been confirmed, indicating that morin exerts its apoptotic effects on CRC cells by inhibiting AKT phosphorylation [5]. Furthermore, in the HT-29 cell line, treatment with morin also activates transforming growth factor- β -activated kinase 1 (Tak1). The Tak1-mediated Hippo signaling pathway has been reported to be associated with the regulation of apoptosis [11]. Additionally, as a non-competitive inhibitor of low molecular weight phosphotyrosine protein phosphatase (LMW-PTP), morin enhances apoptotic sensitivity in HT-29, Caco-2, as well as HCT-116 cells by reducing LMW-PTP levels. This effect is particularly pronounced when combined with 5-fluorouracil. High levels of LMW-PTP were observed in CRC and correlated with apoptosis evasion, tumor progression, and unfavorable prognosis. Moreover, the findings obtained *in vitro* were successfully replicated in Pirc rats [20].

In numerous animal models of CRC, morin has exhibited a remarkable ability to inhibit tumor growth through inducing apoptosis [8, 11]. Specifically, the treatment of morin significantly reduced tumor weight in nude mice (BALB/c *nu/nu*) with CRC induced by subcutaneous injection of COLO205 cells. Moreover, the tumor tissues exhibited elevated levels of p21 and an increased presence of apoptotic cells [11]. It has been reported that p21 inhibits cell proliferation through apoptosis, cell cycle arrest, and DNA damage [11]. Similarly, in the DMH-induced Wistar rats with CRC, morin could promote up-regulation of pro-apoptotic protein BCL2-associated X protein expression and down-regulation of anti-apoptotic protein BCL2 expression in tumor tissues by inhibiting NF- κ B expression, ultimately leading to apoptosis [8]. Additionally, it is noteworthy that the DMH-induced CRC animal model exhibited a significant reduction in cyclooxygenase-2 levels within tumor tissues [8]. The potential enhancement of apoptosis could be attributed to the down-regulation of cyclooxygenase-2 expression.

Apoptosis evasion is a critical hallmark in CRC. Morin, by inducing apoptosis or enhancing apoptosis sensitivity, demonstrates potent pro-apoptotic properties with remark-

able anti-cancer efficacy both *in vitro* and *in vivo* (Table 1).

4.4 Tumor Energy Metabolism

Tumor cells exhibit a higher rate of proliferation compared to normal cells and, as a result, necessitate an elevated uptake of nutrients from the surrounding environment, particularly glucose and glutamine, to fulfill the biosynthetic demands associated with cellular proliferation. Therefore, targeting the uptake and metabolism of glucose and glutamine in tumor cells has been acknowledged as a viable approach for tumor treatment [21].

The transcription factor c-Myc is considered a key driver of glucose and glutamine utilization in tumor cells [21]. Research has indicated that tumor metabolism can be effectively suppressed by morin through the inhibition of the β -catenin/c-Myc signaling pathway, which consequently affects glycolysis and glutamine hydrolysis. As a result, the proliferation of CRC cells and tumor growth are inhibited [6, 13]. In the SW480 cell line, treatment with morin leads to a reduction in facilitated glucose transporter member 1 expression and glucose uptake, thereby exerting an antiproliferative effect by attenuating the Warburg effect [6]. The administration of morin in DMH-induced Wistar rats with CRC resulted in the down-regulation of transporter proteins and metabolic enzymes associated with tumor glucose uptake and glycolysis, including facilitated glucose transporter member 1, hexokinase 2, lactate dehydrogenase A, as well as pyruvate kinase M2. This effect was achieved through the down-regulation of β -catenin and c-Myc expression. Similarly, morin inhibits the c-Myc-mediated up-regulation of glutamine transporter protein neutral amino acid transporter B(0) and glutaminase [13]. Overall, morin suppresses c-Myc-induced tumor energy metabolism (Table 1).

4.5 CSCs

CSCs possess a remarkable capacity for self-renewal, high tumorigenicity, and maintenance of tumor multidirectional differentiation, which are closely associated with resistance to anti-cancer therapy, tumor metastasis, and recurrence in CRC. CSCs in CRC originate from the crypt, and crypt basal columnar cells are considered the true CSCs. Abnormalities in the differentiation process of cryptbasal columnar cells can lead to the development of CRC [22]. CD24, CD133, and CD44 are recognized as markers of CSCs in CRC and significantly contribute to their stemness [14, 22]. Studies have shown that morin inhibits the self-renewal capacity of CSCs by reducing their numbers

and limiting their ability to initiate tumor growth and progression through mechanisms involving the inhibition of pumilio RNA binding family member 1 (PUM1) expression and the blockade of the STAT3 signaling pathway [12, 14].

PUM1 is an RNA-binding protein crucial for maintaining stemness in colorectal CSCs. In the HCT-116 and CT-26 CRC cell lines, morin effectively suppressed CRC cell proliferation, colony formation, and metastasis by down-regulating the expression of PUM1 and CD133, as well as reducing tumorsphere formation. Both tumorsphere formation and CD133 expression are indicative of CSC characteristics. Therefore, it can be deduced that the presence of morin leads to a decrease in both the quantity and functionality of CSCs in CRC through its interaction with PUM1, thereby effectively hindering the cellular proliferation and metastasis of CRC cell lines [14].

The STAT3 signaling pathway is essential for vital biological processes. Upon phosphorylation and activation of STAT3, the phosphorylated form translocates into the

nucleus and regulates target genes transcription [22]. Furthermore, many clinical cases have demonstrated that telomerase activation specifically occurs in colorectal cancer by elongating telomeres in DNA strands to sustain the self-renewal viability of colorectal CSCs. Studies have revealed that morin down-regulates STAT3 phosphorylation, which synergistically enhances its inhibitory effect on telomerase activity when combined with MST-312 (a telomerase inhibitor). By simultaneously targeting STAT3 and telomerase, the combination treatment of MST-312 and morin effectively decreased CD133 levels in HT-29 and SW620 cells, resulting in significant inhibition of the proliferation capacity of CSCs, as well as their ability to form tumorspheres and invade [12]. In conclusion, morin exhibits promising therapeutic potential for targeting CSCs by effectively reducing their quantity as well as self-renewal capacity through targeted inhibition of PUM1 alongside blockade of the STAT3 signaling pathway (Table 1).

Table 1. The anti-cancer mechanisms of morin in research with cell lines and animal models

<i>In vitro</i> studies	<i>In vivo</i> studies	Effects and molecular mechanisms	Reference
/	Colon cancer induced by DMH in male Wistar rats, 50 mg/kg/d, 30 weeks	Inhibition of tumorigenesis by increasing expression of antioxidant and vascular growth factors through activating of the PERK/Nrf2 signaling pathway	[9]
/	Colon cancer induced by DMH in male Wistar rats, 50 mg/kg/d, 30 weeks	Inhibition of tumorigenesis by reducing the oxidative stress	[10]
/	Colon cancer induced by DMH in male Wistar rats, 50 mg/kg/d, 30 weeks	Inhibition of tumor growth by inducing apoptosis as well as decreasing oxidative stress via blocking the NF-κB signaling pathway	[8]
HCT-116, 0~400 μg/ml	/	Inhibition of cell proliferation by inducing apoptosis through Fas receptor up-regulation as well as modulation of BCL2 and IAP family members and ROS generation	[5]
SW480, 50~500 μM	/	Inhibition of cell proliferation by inducing apoptosis through ROS generation and promoting loss of ΔΨ _m , and inhibition of the Warburg effect by decreasing GLUT1 levels	[6]
HT-29 and COLO205, 200 μM	COLO205 cells (5×10 ⁶ cells) were injected subcutaneously into the scapulae of nude mice (BALB/c <i>nu/nu</i>), 10/20 mg/kg/d, 2 weeks	Inhibition of cell proliferation by inducing apoptosis through ROS generation, caspase-3 cascade activation and p21 levels up-regulation	[11]
HT-29 and SW620, 50 mM	/	Inhibiting the STAT3 signaling pathway leads to increased phosphorylation levels of p53 and BAD, resulting in the inhibition of CSCs, suppression of cellular invasiveness, induction of apoptosis, and improved sensitivity to 5-FU	[12]

HT-29 and HCT-116, 15~60 mg/L	HCT-116 cells (1×10^6 cells) were injected subcutaneously into the flanks of nude mice (BALB/c <i>nu/nu</i>), 30/60 mg/kg/d, 3 weeks	Repression of cellular proliferation and neoplastic growth through inhibition of the NF- κ B signaling pathway	[7]
/	Colon cancer induced by DMH in male Wistar rats, 50 mg/kg/d, 30 weeks	Inhibition of tumor growth by affecting glycolysis and glutamine hydrolysis in tumor cells through inhibiting the β -catenin/c-Myc signaling pathway	[13]
HCT-116 and CT-26, 50~400 μ M	/	Reduction of CSCs and inhibition of colon cancer cell proliferation, colony formation, migration, and tumorsphere formation by suppression of PUM1 levels	[14]
HT29, HCT-116, and Caco2, 1.5 μ M	Pirc (F344/NTac-Apc ^{am1137}) rats, 50 mg/kg/d, 2 weeks	Increasing sensitivity of drug-resistant cells to 5-FU by down-regulating LMW-PTP levels	[20]

Abbreviation: DMH, 1,2-dimethylhydrazine; PERK/Nrf2, PRKR-like endoplasmic reticulum kinase/Nuclear factor erythroid 2-related factor 2; NF- κ B, nuclear factor kappa-B; BCL2, B-cell lymphoma-2; IAP, inhibitor of apoptosis protein; ROS, reactive oxygen species; $\Delta\Psi_m$, mitochondrial membrane potential; GLUT1, facilitated glucose transporter member 1; CSCs, cancer stem cells; 5-FU, 5-fluorouracil; BAD, BCL2 associated agonist of cell death; STAT3, signal transducer and activator of transcription 3; PUM1, pumilio RNA binding family member 1; LMW-PTP, low molecular weight phosphotyrosine protein phosphatase.

5. Conclusion

Given the high morbidity and mortality rates associated with CRC, as well as the issue of drug resistance, it is imperative to explore more efficient therapeutic strategies. Morin has been demonstrated to exhibit significant anti-cancer efficacy in CRC cell lines and animal models. Furthermore, morin acts as an inhibitor of certain metabolic enzymes and efflux transporters, thereby enhancing the effectiveness of other anti-cancer drugs. These properties place morin in a unique position in the field of colorectal cancer treatment, with a high potential for drug development, either alone or in combination with other therapies. Over the past two decades, numerous studies have elucidated various anti-cancer mechanisms of morin in CRC, including modulation of ROS levels, induction of apoptosis, reduction of tumor energy metabolism, and inhibition of CSCs. However, there may be other more extensive and profound mechanisms about morin, and thus, further mechanistic studies are warranted. Clinical trials on the effectiveness and safety of morin are still lacking, even though both *in vitro* and *in vivo* investigations have

suggested the anticancer profits in CRC. Therefore, conducting relevant clinical trials is crucial to validate the safety and efficacy profile of morin when used as monotherapy or combined with chemotherapeutics or targeted therapies.

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