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Review Article

MOLECULAR MECHANISM AND THERAPEUTIC POTENTIAL OF BERBERINE, BAICALEIN, ORIDONIN IN THE TREATMENT OF COLORECTAL CANCER – A REVIEW

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ABSTRACT

The aim of this research is to assess the effect of berberine and baicalein and oridonin (ORI) treatment on colorectal cancer (CRC) cells. The research examines how these compounds bring about cellular alterations, stop the cell cycle progression, and trigger cell death. The cancer-fighting agents berberine and baicalein together with ORI demonstrate strong anticancer properties against CRC tissues through metabolic instability and cell cycle arrest leading to apoptosis. ORI affects the activation of TP53/TCF4 mechanisms which creates endoplasmic reticulum stress and then leads to higher reactive oxygen species production alongside calcium ion imbalances. The retinoid X receptor alpha activation mechanism performs better than berberine in colon cancer cell growth inhibition. Berberine suppresses CRC progression through its ability to influence the transforming growth factor-beta signaling pathway together with its inhibitory action on epithelial-mesenchymal transition and its weakening effect on colorectal liver metastasis. The altered composition of gut microbes reduces tissue tumorigenesis as well as total microbial abundance. Berberine shows its anti-metastatic capabilities by blocking the actions of matrix metallopeptidase (MMP)-2 and MMP-9 enzymes which play important roles in cancer cells spreading during metastasis. The suppression of CRC cell growth occurs through berberine-mediated G2/M cell cycle arrest and cell death mechanism that results in cyclin B1 and cdc2 and cdc25c protein downregulation. The anticancer and anti-inflammatory agent baicalein acts as a major element in developing tumorous lesions associated with colitis. The compound speeds up G2/M phase cell cycle arrest through its role in regulating the toll-like receptor 4/nuclear factor-kappa B signaling pathway in HT-29 colon cancer cells. The regulatory mechanisms of this process decrease tumorigenesis that stems from inflammation while also restricting CRC cell multiplication.

Keywords: Colorectal cancer, Molecular pathway, Berberine, Baicalein, Oridonin.

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INTRODUCTION

The disease known as colorectal cancer (CRC) represents a leading worldwide cause of cancer-related fatalities [1]. Structural progress in early screening and treatment has not eliminated CRC's status as a major health issue caused by treatment-resistant cells along with delayed detection of dangerous tumors. Medical procedures that use chemotherapy alongside radiation and surgery produce severe side effects as well as treatment failure [2]. The urgent need exists for alternative treatment methods which attack various oncogenic pathways.

Natural compounds derived from medicinal plants have gained attention for their potential anticancer properties. Bioactive compounds such as berberine, baicalein, and oridonin (ORI) have shown promising effects against CRC by modulating key molecular pathways. These compounds exhibit multiple mechanisms of action, including apoptosis induction, cell cycle arrest, tumor growth inhibition, and suppression of metastasis. In the non-surgical oncology specialism, there are a number of healthcare professionals with unique knowledge and skills [3].

Berberine, isolated from *Coptis chinensis*, regulates various signaling pathways such as Adenosine monophosphate-activated protein kinase (AMPK)/the mechanistic (or mammalian) target of rapamycin (mTOR)/Unc-51-like kinase 1 (ULK1), leading to tumor suppression, autophagy, and apoptosis. In addition, it inhibits the epidermal growth factor receptor (EGFR) pathway, reducing cancer cell proliferation and enhancing the efficacy of conventional therapies [4]. Berberine also modulates oxidative stress and inflammatory responses, further interfering with CRC progression [5].

Baicalein isolated from *Scutellaria baicalensis* regulates cell cycles, induces apoptosis, and inhibits metastasis by targeting matrix metallopeptidase (MMP)-2/-9, protein kinase B (AKT), and nuclear factor-kappa B (NF-κB) pathways. They arrest tumor growth in G1/S and G2/M phases, activate caspase-3/-9, and enhance chemotherapy effectiveness. Baicalein suppresses the mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinase (ERK) and Wnt/Notch pathways, preventing cancer progression and promoting senescence.

ORI, a diterpenoid isolated from *Rabdosia rubescens*, exhibits strong cytotoxic effects on CRC cells by disrupting metabolic pathways essential for cancer survival. It activates the AMPK/mTOR/ULK1 pathway, leading to autophagy and apoptosis. ORI also downregulates oncogenic proteins such as cellular myc (c-Myc) and glucose transporter 1 (GLUT1), reducing tumor cell proliferation and enhancing therapeutic outcomes [6].

CRC development is driven by dysregulated signaling pathways, including EGFR/MAPK, phosphoinositide-3-kinase (PI3K)/AKT, Notch, transforming growth factor-beta (TGF-β), and Wnt/β-catenin. These pathways control cell proliferation, differentiation, apoptosis, and metastasis. The PI3K/AKT pathway, frequently activated in CRC, enhances cancer cell survival and resistance to therapy. Similarly, the Wnt/β-catenin pathway promotes cancer stem cell renewal and tumor

growth. Targeting these pathways with plant-derived compounds offers a promising approach to CRC treatment [7].

CRC

The risk of dying from cancer is high because its origin point is in the large intestine, followed by hepatic spread [8]. Colon cancer produces various health consequences that extend beyond the gastrointestinal functions of both male and female bodies. Modern cancer prevention through chemoprevention uses natural dietary elements that block cancer development and decrease tumor expansion when they drive regression. Several scientific investigations have examined flavonoids alongside carotenoids, alkaloids, and organosulfur compounds as phytochemicals while assessing spices, tea-derived ingredients, herb-related components, and fruit and vegetable extracts for their potential as chemo-preventive agents [9]. The disease known as CRC represents a leading worldwide cause of cancer-related fatalities [10]. Structural progress in early screening and treatment has not eliminated CRC's status as a major health issue caused by treatment-resistant cells along with delayed detection of dangerous tumors [11]. Medical procedures that use chemotherapy alongside radiation and surgery produce severe side effects as well as treatment failure [12]. The urgent need exists for alternative treatment methods which attack various oncogenic pathways. It has also been demonstrated that NFκB is activated by PI3K/AKT pathway activation through IKK phosphorylation, which phosphorylates IκBα and RELA/p65. A key factor in colorectal carcinogenesis is the interrelated Ras/ERK, PI3K/AKT, and NFκB pathways [13].

Polyps

The inner lining of the colon or rectum develops polyps which eventually turn into colorectal tumors. Adenomas as well as adenomatous polyps serve as the two known categories of colon polyps that exist. The most common type of adenomatous polyp is tubular adenoma among the three possible types of adenomas. The most commonly found type of adenomatous polyp exists in villous form (Fig. 1).

Hyperplastic polyps, along with inflammatory polyps, form the most frequently occurring types of polyps; yet they generally stay non-cancerous. Individuals with hyperplastic polyp sizes larger than 1 cm may require more frequent CRC screenings using colonoscopy. Sessile serrated polyps, along with traditional serrated adenomas, usually receive adenoma-type treatment since they display increased cancer transformation tendencies [14].

Stages of CRC

Healthcare providers may classify this condition as carcinoma *in situ* during their assessments. At this point of discussion, they describe abnormal or precancerous cells that exist in your mucosa, which forms the innermost part of your colon wall (Fig. 2). Shows Stage I CRC extends through parts of the intestine wall without reaching close lymph nodes or penetrating the outer muscular coat, cancer spreads throughout most of the intestine wall at this point but does not reach surrounding lymph nodes. The three types of Stage II colon cancer include Stage IIA through Stage IIC. Stage IIA colon cancer has reached throughout most of the colon wall without breaking through to the outer layer. The cancer extends to either the outer colon wall layer or penetrates through the wall. During Stage IIC, cancer spreads to adjacent organs without spreading to lymph nodes. The spread of cancer to lymph nodes characterizes the Stage III classification of colon cancer. Stage III colon cancer has three subcategories that share similar characteristics with Stage II colon cancer. Stage IIIA indicates sheet-like or deep colon wall cancer that is distributed to zero to four lymph nodes. Stage IIIB defines the condition in which cancer spreads to multiple layers of your colon wall yet stops at a maximum of three lymph nodes. Stage IIIB colon cancer describes cancer that spreads to four or more lymph nodes even if it affects fewer layers of the colon wall. Stage IIIC involves colon cancer spreading to the outer layer as well as the next outer layer, affecting at least four lymph nodes. Stage IIIC colon cancer arises from the tumor's spread to nearby organs together with one or multiple lymph node involvements. The fourth stage of colon cancer development occurs when the cancer spreads to other body regions, including the liver, lungs, and ovaries. The cancer spreads beyond one organ and affects lymph nodes that exist in distant locations away from the colon during Stage IVA. Stage IVB colon cancer indicates that cancer spreads to more than one distant organ and additional lymph nodes. Cancer spreads to distant organs as well as causing damage to lymph nodes together with abdominal tissue during stage IVC [15].

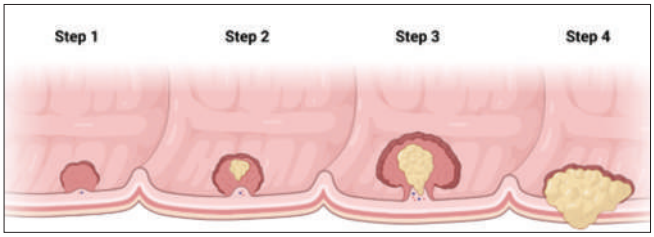

Fig. 1: Development of polyps in colorectal cancer

Mechanism of CRC

(Fig. 3) shows that imbalance in gut bacteria (dysbiosis) leads to inflammation, DNA damage, and oxidative stress (reactive oxygen species [ROS]), causing colon cancer through genetic mutations and chronic inflammation. Harmful bacteria, bile acids, and toxins disrupt the gut lining, triggering immune responses that promote tumor growth [16].

SIGNALING PATHWAYS INVOLVED IN COLON CANCER

EGFR and MAPK

Fig. 4 shows the epidermal growth factor (EGF) binds to its receptor (EGFR), leading to receptor activation and autophosphorylation of tyrosine kinase. This triggers a signaling cascade where Grb2 binds to phosphorylated EGFR, activating SOS, which converts GDP to GTP, activating RAS, leading to the sequential activation of Raf, MEK, and ERK, ultimately regulating cellular responses.

Mechanism involved in EGFR and MAPK

EGFR becomes activated upon epidermal growth factor (EGF) binding, leading to tyrosine phosphorylation and Grb-2 binding (Fig. 4). This activation triggers RAS, which initiates a kinase cascade, ultimately activating ERK (MAPK) to regulate various cellular functions. ERK further influences transcription by phosphorylating c-Fos and c-Jun, forming the AP-1 complex, and modifying the S6 protein. The pathway is regulated through SOS inhibition, myelocytomatosis oncogene (MYC) regulation, and RAS inactivation through GAP proteins, ensuring controlled signal transmission [17].

Fig. 5 the EGFR/MAPK signaling cascade starts when epidermal growth factor receptor (EGFR) becomes activated following its interaction with EGF after which it produces tyrosine residue phosphorylations. Elastin-binding protein Grb-2 collaborates with SOS proteins in order to activate RAS by changing GDP to GTP. The dynamic RAS begins a phosphorylation cascade that phosphorylates Raf to activate MEK and ERK subsequently. After activation by phosphorylation MAPK (ERK) controls cell functions by activating transcription factors AP-1 along with CREB and MYC which promote gene expression. GAP regulatory proteins bring an end to signaling by transforming active RAS-GTP into inactive RAS-GDP.

Notch signaling pathway

The Notch signaling pathway functions as a widely preserved intercellular communication method. A healthy intestine depends on Notch signaling for sustaining the intestinal lining structure and controlling stem cell differentiation while fostering goblet formation [18] (Fig. 6). Incorrect functionality of this pathway leads to CRC development. The signaling mechanism consists of five ligands that include Jagged-1 and Jagged-2 alongside Delta-like-1 along with Delta-like-3 and Delta-like-4 and four receptors referred to as Notch-1, Notch-2, Notch-3, and Notch-4 which operate alongside genes named

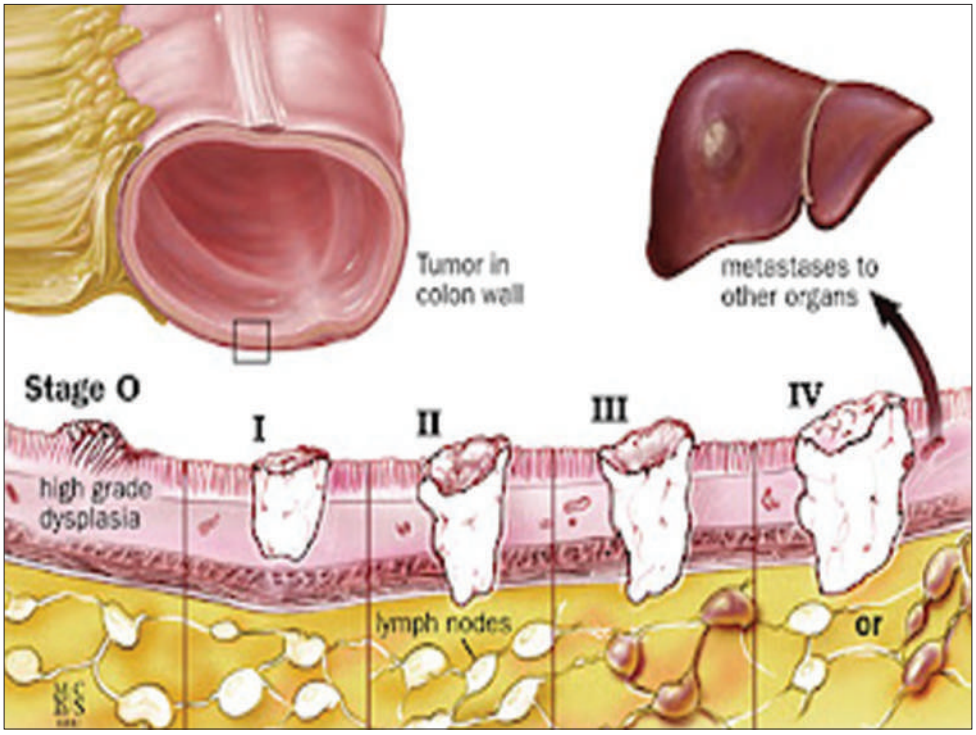

Fig. 2: Colorectal cancer stages

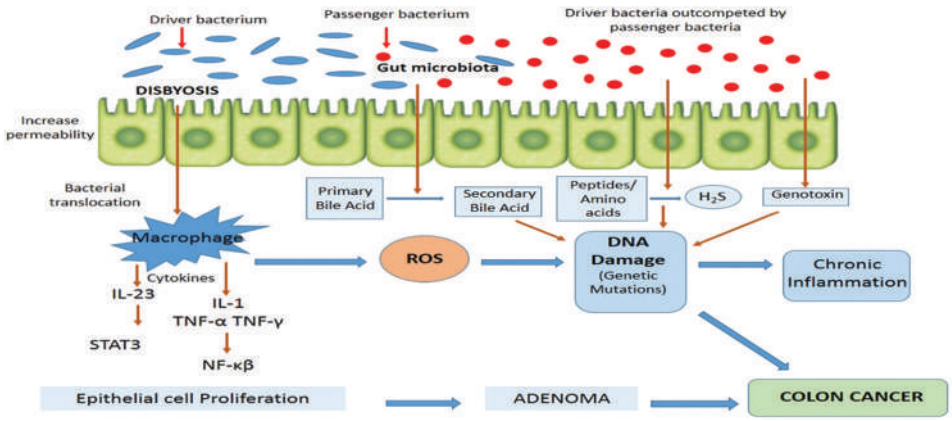

Fig. 3: Mechanism of colorectal cancer

P21, Hes-1, and Deltex [19,20]. Normal cell development requires the Notch pathway together with essential functions that enable cell differentiation and proliferation in addition to apoptosis.

Notch-1 increases CRC cell growth; it mostly acts as an oncogene (cancer-promoting), but in rare cases, it can suppress survival due to the formation of new blood vessels (vasculogenesis). It encourages epithelial-mesenchymal transition, masking cancer cells likely to spread (metastasize). 40–50% of CRC patients develop metastases [21].

Notch 1 interacts with SLUG, SNAIL, and TGF-β to create cancer and works with Jagged-1 and Notch 3 to make CRC cells more stem cell-like, making the disease harder to treat. It promotes CRC by controlling the cell cycle (P21) and apoptosis (p53-upregulated modulator of apoptosis genes).

PI3K/AKT signaling pathway

Research indicates that colon cancer cells trigger PI3K/AKT activation through Src protein tyrosine kinase activation [22]. The inhibitory mechanism of mTOR by adiponectin works as one of the downstream targets within the PI3K/AKT signaling pathway [23]. Within the cellular environment, PI3K/AKT functions as an intracellular signaling pathway which regulates growth processes as well as proliferation and glucose metabolic activity. The cellular action of phosphatidylinositol-4,5-bisphosphate into phosphatidylinositol-3,4,5-trisphosphate arises through the enzyme lipid kinase PI3K which activates AKT to produce multiple functional cellular responses [24].

The NF-kB increases cell survival and tumor cell resistance to apoptosis and regulates its angiogenesis and invasiveness (Fig. 7). NF-kB is a transcription factor and downstream targets phosphorylated by PI3/AKT to upregulate cellular survival signal pathways. In the cytoplasm, it complexes with IkB; AKT phosphorylated and degrades it, regulating gene transcription when NF-kB enters the nucleus [25]. PI3K/AKT regulates the Fas/Fas ligand system (cellular apoptosis), which is a TNF receptor family recruitment of Fas-associated death domain and activation of the caspase cascade. This system produces cell apoptosis [26]. Fas is decreased in colon cancer by promoting Fas ligand when PI3K/AKT

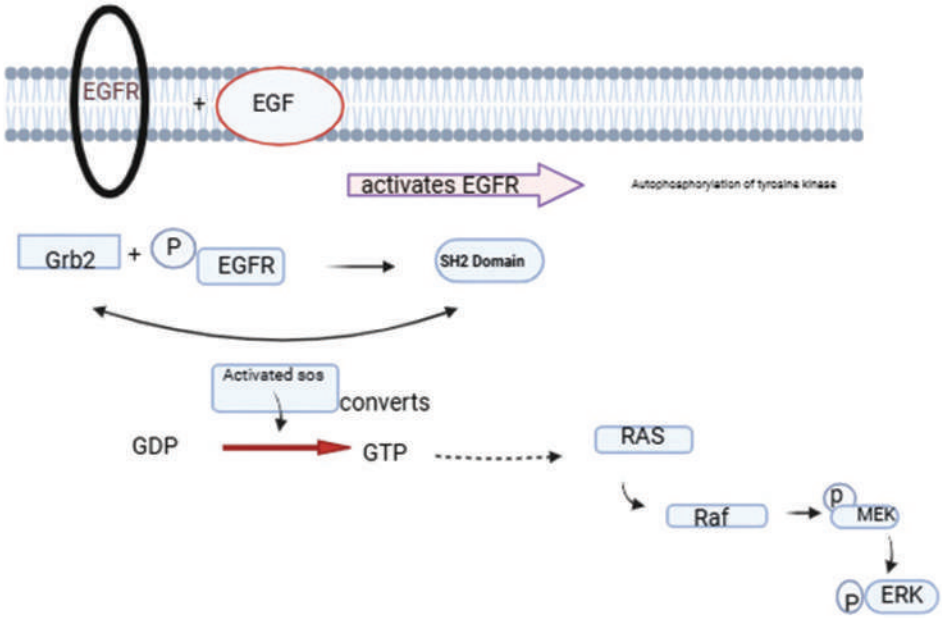

Fig. 4: Schematic representation epidermal growth factor receptor and the mitogen-activated protein kinase pathway

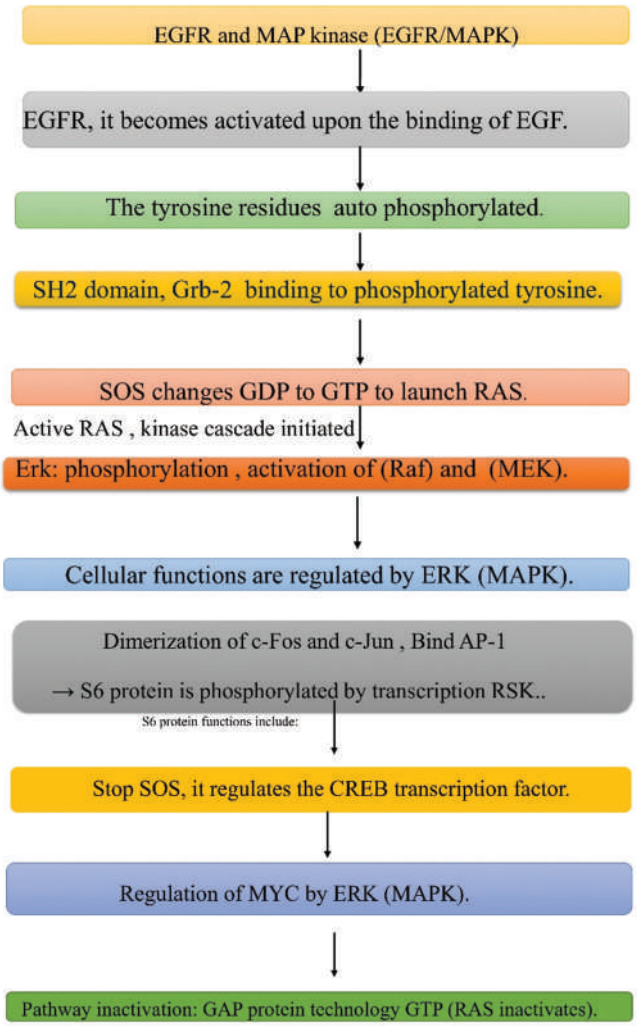

Fig. 5: Actions of epidermal growth factor receptor and the mitogen-activated protein kinase pathway involved in colon cancer

blocks forehead proteins [27], PI3K/AKT upgrades colon cancer to increase cell proliferation; it promotes cyclin D3 (inhibits inflammation) and MYC to increase cell cycle deactivation of glycogen synthase kinase 3 [28]. In colon cancer cell line 320, small interfering RNA inhibits MYC, resulting in decreased replication and proliferation of DNA [29]. In G1/S transition, the cell cycle is blocked by a decrease in P27Kip1 (P27) and P130Rb2 (P130), which shows reduced colon cancer where there is a decrease in adipocyte hyperplasia during P27 promoted by AKT, inhibiting fork head protein [30]. The PI3K pathway activates mTOR through increased protein synthesis for cell growth activation. mTOR regulates cell growth and metabolism by activating 70 kDa ribosomal S6 kinase, after which translocation becomes initiated and elongation occurs, but mTOR inhibits elongation. The binding of initiation factor 4E binding protein together with inhibitory protein is necessary for this process to take place. CRC development and progression depend on the essential pathway that involves PI3K/AKT/mTOR.

Cells use the PI3K/AKT/mTOR pathway as their main signaling system because it enables control over vital cellular processes such as survival, along with growth and division functions. Several factors, including insulin, sonic hedgehog EGFs, calmodulin, and IGF-1, can activate this pathway, while Phosphatase and tension homolog deleted on chromosome 10, Glycogen synthase kinase-3 beta, and HB9 are among its antagonistic molecules. The cellular equilibrium depends on this pathway, and it remains vital for developing cancer, particularly CRC. CircIL4R, together with metabolites, augments CRC cell progression and PI3K/AKT signals activated. The treatment response of cancer cells to radiation and chemotherapy, as well as nutrient stress, becomes stronger when particular elements of the PI3K/AKT pathway receive targeted blocking. Medical experts suggest implementing simultaneous MAPK and PI3K/AKT inhibitor treatments, given that MAPK inhibition minimizes autophagy-related psoriasis. The cellular process of autophagy enables cells to clean waste products and damaged components, which preserves a healthy environment throughout the gut. Estrogen-related receptor α (ERRα) and gut bacteria, along with ERRα, regulate the mechanisms that defend cells from inflammation and safeguard mitochondria from damage [31].

Wnt/B-catenin determinant of cell's fate

Entire intestinal stem cells located in crypts of the little intestine and large intestine work together to reconstruct depleted differentiating intestinal epithelium cells through rapid cell renewal (Fig. 8). Intestinal

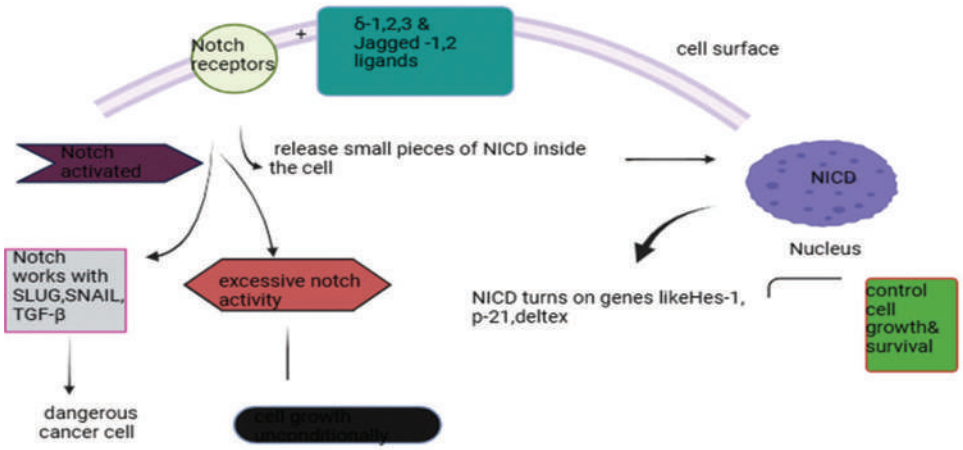

Fig. 6: Notch signaling pathway involved in colon cancer

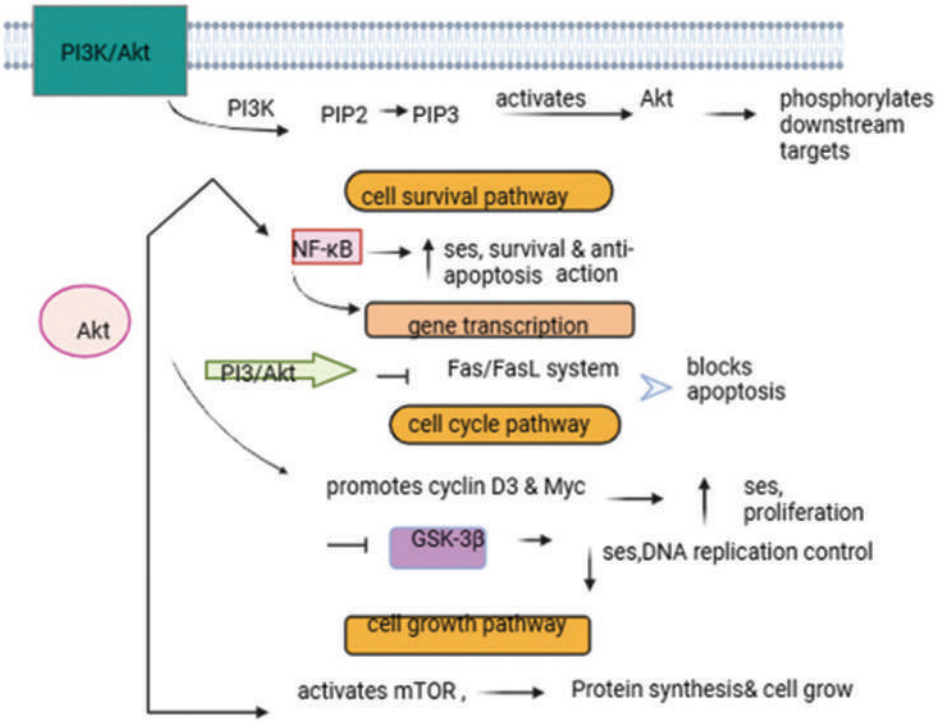

Fig. 7: Schematic diagram of phosphoinositide-3-kinase/protein kinase B signaling pathway

stem cell deficiency, together with suspended proliferation, occurs when Wnt/β-catenin pathway activity reaches its maximum level at the crypt base, therefore resulting in elimination of the intestinal epithelium [32]. The number of intestinal stem cells increases under Wnt signaling potentiation because Wnt signaling serves as a fundamental mechanism for both ISC self-renewal and proliferation during homeostasis [33]. Normal colonic epithelial cells evolve into malignant CRC through multiple genetic changes within more than 10 years while maintaining their association with the Wnt/β-catenin signaling pathway [34]. Sporadic CRCs show 80% argon plasma coagulation *(APC)* gene mutations because the *APC* gene functions as the primary cause of FAP familial adenomatous polyposis syndrome. The early-stage CRC tumors develop primarily from *APC* genetic and β-catenin along with Axin mutations. Research demonstrates that the Wnt signaling pathway controls CRC stem cell (CSC) self-renewal processes which occur within the intestinal crypt. Through self-renewal, CSCs generate both new CSCs and tumorous cells found in the bulk cellular mass of the cancer. The binding of p300 with β-catenin enables CSC differentiation while CREB-binding protein combined with β-catenin promotes the maintenance of CSC potency [35]. The resistance of standard chemotherapeutic agents reportedly affects genes including Lgr5, CD44, CD24, CD133, ABC cassette genes, and EpCAM, which Wnt signaling targets. Restoration of APC function shows promise in CRC therapy because it enables proper crypt maintenance even when TP53 and Kirsten rat sarcoma viral oncogene homolog mutations exist. CRC treatment could benefit from Wnt/β-catenin inhibitors because studies demonstrate that improper Wnt/β-catenin regulation causes CRC [36].

Table 1 shows EGFR/MAPK activation triggers a kinase cascade with ERK regulating cell survival via AP-1 and MYC, while Notch signaling defends the intestinal wall and, when dysregulated, drives colorectal cancer and EMT metastasis. PI3K/Akt together with NF-κB enhances cell proliferation and metabolic growth by resisting apoptosis via Fas/FasL, whereas Wnt/β-catenin maintains normal and cancer stem cells—APC restoration being a potential CRC therapy.

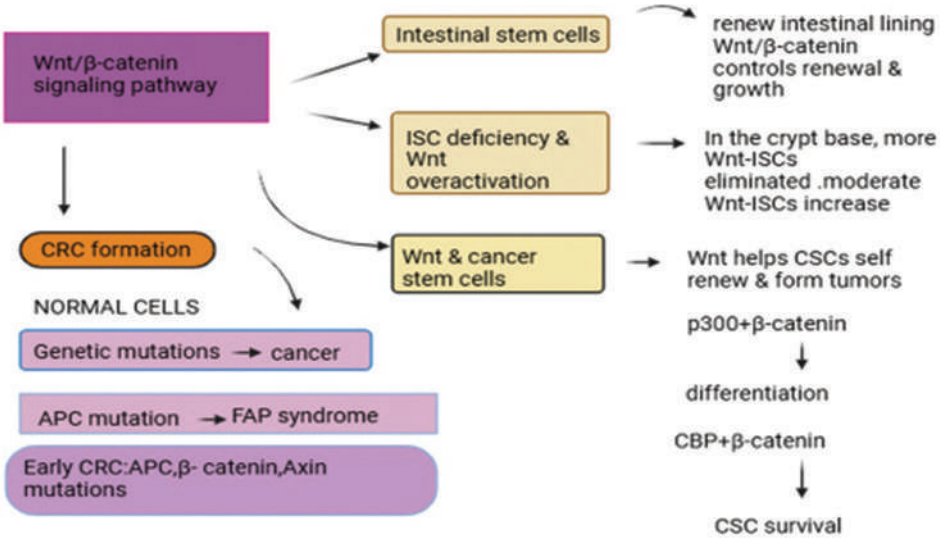

Fig. 8: Wnt pathway schematic representation

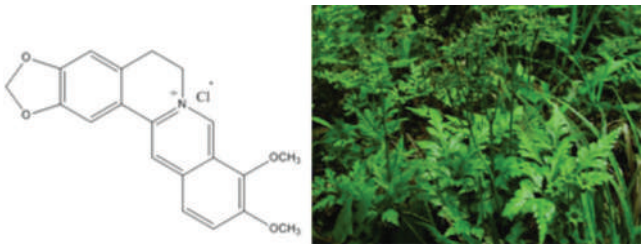

Fig. 9: *Coptischinensis*. Structure of berberine

BERBERINE

Berberine is an alkaloid (Fig. 9) that was isolated from *C. chinensis* (family *Ranunculaceae*), a plant used in traditional Chinese medicine. It has anti-infectious properties and anti-inflammatory has been used to treat hypertension and diabetes [37]. Most recently, it was discovered that berberine had an anti-tumor effect by altering the expression of MMP-2/-9; however, the underlying molecular mechanism is yet unknown [38].

The anti-CRC effect of berberine and its mechanism

Berberine prevents human colorectal adenocarcinoma development both in test tube cultures and animal models. G1/S and G2/M cell cycle arrest becomes activated through checkpoint protein expression dependence during this inhibition process. Berberine stops colorectal adenocarcinoma development through G2/M phase arrest combined with cyclin B1, cdc2, and cdc25c expression suppression [39]. Pre-clinical evidence shows that berberine triggers cyclooxygenase-2 (COX-2) reduction and migration while regulating cancer and cell proliferation and apoptosis. Berberine showed its ability to decrease the expression and proliferation of EGFR in colon epithelial cells through enhancing Cbl activity levels [40]. Experimental data shows berberine demonstrates its potential to trigger cell death along with controlling the growth of cells and decreasing inflammation of cancer cells in the colon. The SW480 cell cycle shows evidence of coming to a halt at the G2/M phase because of berberine treatment. Several biochemical events included cytochrome c and poly (ADP-ribose) polymerase cleavage release into the cytosol together with caspase and Bcl-2 family protein activation and mitochondrial membrane potential loss [41]. Berberine demonstrates dual functionality by inhibiting cancer cell growth while forcing cells to undergo apoptosis and by reducing CRC development risk. Protein expression levels under berberine control determine these outcomes [42]. Berberine functions as a down-regulator against COX-2 messenger RNA (mRNA) and protein expression while suppressing cancer cell development. Multiple research studies demonstrate that peroxisome proliferator-activated receptor gamma (PPARγ) activates apoptosis in addition to inhibiting it during cancer of the colon [43]. Colon cancer prevention and treatment will likely use PPARγ as a breakthrough therapeutic target. Berberine reduces PPARγ mRNA expression in Lovo cells, inhibiting Lovo cell growth, programmed cell death, and growth inhibition of colon cancer Lovo cells. The control of cellular homeostasis through tyrosine kinase EGFR influences angiogenesis.

Berberine has been identified as a new retinoid X receptor alpha (RXRα) activator

Studies show that berberine given orally decreased colon polyp formation and recurrence in APC min/+ mice as well as in patients with familial adenomatous polyposis through mechanisms that reduced β-catenin protein located in cell nuclei. Our hypothesis suggests that berberine controls β-catenin levels through the APC-independent retinoid X receptor (RXR) agonist/RXR pathway since numerous key APC pathway genes harboring mutations exist in colon cancer instances [44]. The bond between berberine and RXRα facilitates suppression of β-catenin signaling as well as inhibition of colon cancer cell–cell differentiation. Scientific research studies the influence of RXRα binding on β-catenin signaling activity and KM12C cell proliferation rates to determine the RXRα activating mechanism of berberine [45]. Through activation of RXRα protein activity, berberine demonstrates the ability to stop KM12C cell multiplication and therefore decreases proliferating cell nuclear antigen (PCNA) production. RXRα mediates the inhibitory impact of berberine on colon cancer cell proliferation and β-catenin signaling. The cell cycle reaches its G2/M phase because berberine forces KM12C cells together with other colon cancer cell varieties into growth arrest. Furthermore, berberine strengthens RXRα and β-catenin binding interactions which leads to lower β-catenin protein amounts. Leupeptin did not affect RXRα inhibitory activity thus indicating that the proteins undergo degradation through proteasome-dependent pathways. The binding of berberine to RXRα promoted advanced protein interaction structures and enhanced β-catenin breakdown patterns but these functions diminished with RXRα mutant controls. The binding action of berberine with RXRα protects colon cancer anti-proliferative function by producing an enhanced RXRα-β-catenin bond complex. The degradation mechanisms of β-catenin inside colon cancer cells achieve better results through berberine activation of the RXRα receptor which enhances c-Cbl expression. The treatment promotes β-catenin nuclear breakdown that ends up as proteasome degradation but it operates

Table 1: Main pathways involved in colon cancer and their mechanism of action

Pathways	Mechanism	References
EGFR/MAPK Pathway	A succession of protein kinases starts with EGFR activation because it activates the EGFR/MAPK Pathway. The ERK protein belongs to the growth protein family that belongs to MAPK and controls cell survival and division through its regulatory pathways. When AP-1 regulates activity c-Jun enables the formation of transcription-active c-Fos dimers. Myelocytomatosis oncogene is under ERK regulation-The function of proteins becomes inactive as GAP proteins participate in the process.	[17]
Notch Signaling Pathway	Notch signaling performs a dual function by defending the intestinal wall while controlling stem cell multiplication. CRC development starts first with a condition of dysregulation. During cancer development the Notch1 protein demonstrates both tumor-regulatory functions and acts as an oncogene. The signaling pathway that begins epithelial-mesenchymal transition enables metastasis to happen.	[21]
PI3K/AKT Pathway	Both PI3K/AKT pathway and NF-κB pathway promote cell proliferation alongside enhancing glucose metabolic functions and growth but NF-κB also protects cells from programmed death. The apoptosis system becomes more resistant to death through protein interactions between Fas and Fas ligand.	[31]
Wnt/β-Catenin Pathway	The Wnt/β-Catenin signaling pathway maintains intestinal stem cells through their normal proliferative and differentiation functions to avoid 80% of sporadic CRC cases in patients with APC defects. During cell replacement, the Wnt signaling pathway maintains cancer stem cells through their protection which results from *Lgr5*, *CD44*, and *CD24* gene activity and other related biological factors. Evidence suggests that APC restoration can serve as a therapy for CRC management.	[35]

MAPK: The mitogen-activated protein kinases, ERK: Extracellular signal-regulated kinase, PI3K: Phosphoinositide-3-kinase, AKT: Protein kinase B, EGFR: Epidermal growth factor receptor, CRC: Colorectal cancer

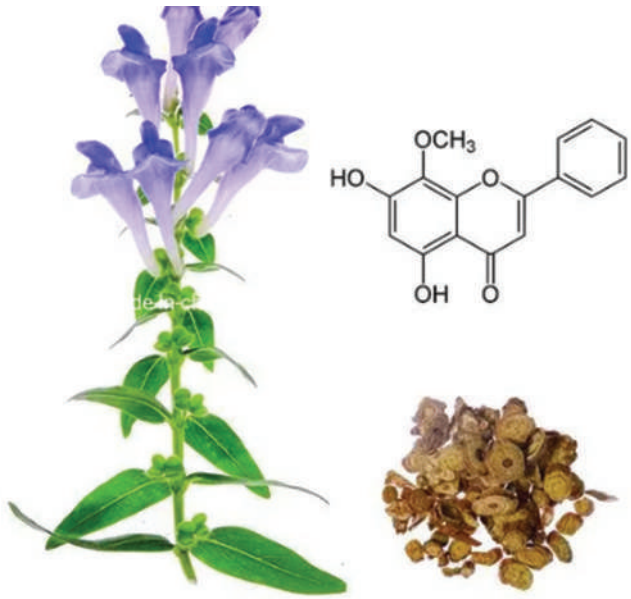

Fig. 10: ***Scutellaria baicalensis***

in reverse to the activities of Leptomycin B [45]. Berberine reduces cyclic adenosine monophosphate (cAMP)-induced chloride secretion in T84 human colonic carcinoma cells through inhibition of basolateral potassium voltage-gated channel subfamily Q member (KCNQ1) channels. The KCNQ1 potassium channel struggles to work as intended in T84 human colonic cells because berberine activates a protein-dependent process to stop this potassium channel that regulates cAMP-dependent Cl-secretion leading to blocked transportation of Cl- through colonic epithelia. The T84 cells express two K+ channels that function through Ca2+ elevation in the cytosol yet another channel operates under cAMP-dependent agonist stimulation. Under normal conditions, the KCNQ1 channel determines the approximate amount of secretion movement through the colon. The administration of berberine reduced K+ conductance in T84 human colonic basolateral membranes under forskolin stimulation so it became sensitive to Ba2+ and chromanol 293B and HMR-1556 blockade. The blood glucose-lowering mechanism of berberine depends on its activation of p38 MAPK and AMP-activated protein kinase in tissues to block KCNQ1 channels at basolateral membranes thus producing antisecretory effects which suppress cAMP-stimulated conductance and apical Cl− conductance and preserve Na+–K+-ATPase pump activity and apical Cl− conductance. Berberine targets cyclin-dependent kinases during its action but also restricts MAPK pathway signaling pathways while presenting an antiproliferative effect. Berberine disrupts the EGF signaling pathway thus producing limited Cl− secretion together with reduced antiproliferative results. PKCα functionality enables the activation process of PKA and PKCα in addition to p38 MAPK. Two protein kinases exercise short-term control after berberine activates the KCNQ1 channel before channel regulation takes place. The antisecretory effect in females occurs because berberine prevents KCNQ1 channel expression in the body. The reduction of secretion by berberine was decreased by kinase inhibitors HBDDE and SB202190 which worked as independent agents. A laboratory test validated that berberine disrupts K+ movement in T84 cells which leads to reduced Cl− epithelial tissue transport. After berberine treatment, PKA becomes activated to promote the functioning of CFTR within colonic crypt cells. The drug blocks the release of chloride ions but does not change the activity of apical chloride ions. The controlled cAMP–PKA pathway regulates cAMP levels by creating localized cAMP microdomains that explain such paradoxical effects [46].

Table 2 shows Coptis chinensis (Goldthread) yields berberine, an alkaloid traditionally used for its anti-inflammatory, anti-infectious, anti-diabetic, and antihypertensive effects, which induces G1/S and G2/M cell cycle arrest, reduces COX-2 to block migration and downregulates EGFR via Cbl to trigger caspase-mediated apoptosis.It acts through multiple pathways: regulating the cell cycle via cyclin B1/B2 and β-catenin destruction, suppressing PPARγ RNA to curb LoVo cell growth, and activating MAPK/AMPK to alter glucose metabolism and limit proliferation.

BAICALEIN

Baicalein (7-D-glucuronic acid-5, 6-dihydroxyflavone; C21H18O11) isolated from *S. baicalensis* traditional Chinese roots, family of *Lamiaceae* (mint) (Fig. 10). Biological actions of baicalein include

Table 2: Characteristics of active constituents of berberine

Category	Pathway and Uses	References
Biological source	*Coptis chinensis* (Goldthread)	[37]
Active Compound	Berberine (alkaloid)	[37]
Traditional Uses	Anti-inflammatory, anti-infectious, anti-diabetic, antihypertensive	[37]
Anti-colorectal cancer mechanism	Cell cycle arrest which occurs during G1/S and G2/M phases. The reduction of cyclooxygenase-2 expression blocks cell migration together with preventing inflammation. The protein Cbl lowers cell epidermal growth factor receptor amounts while initiating apoptosis by activating caspases and releasing cytochrome-c and breaking poly (ADP-ribose) polymerase.	[39]
Pathways involved	Cell cycle regulation: The G2/M phase arrest function depends on three factors: cyclin B1 protein regulation and cyclin B2 protein regulation alongside β-catenin destruction. PPARγ regulation: PPARγ Regulation the method turns off PPARγ RNA expression thus halting LoVo cell population growth. MAPK/AMPK activation: The activation of MAPK/AMPK leads to changes in cell glucose metabolism along with a reduction in cell-growing capabilities.	[46]

AMPK: Adenosine monophosphate-activated protein kinase, MAPK: The mitogen-activated protein kinases, PPARγ: Peroxisome proliferator-activated receptor gamma

its regulatory effects on cell cycles through cyclin regulation of CDKs [47] and its antioxidant capacity to remove reactive radicals with simultaneous reduction of MAPK and AKT along with mTOR activities [48] and its ability to activate apoptosis through functionally active caspase-9/-3 [49] while restraining MMP-2/-9 expression [50] to inhibit invasion and metastasis.

S. baicalensis has a cold nature and a bitter taste, attributed to the lung, spleen, gallbladder, small intestine, and large intestine meridians. In general, it has been used to clear heat and dry dampness, prevent miscarriage, cool blood, remove toxins, and discharge fire in traditional Chinese medicine [51].

***In vivo* CRC studies of baicalein**

Mice administration of azoxymethane (AOM) and dextran sodium sulfate (DSS) Induced Colon Cancer: Oral route 1, 5, 10 mg/kg body weight for 16 weeks. Baicalein prevents cancer growth in colon models while decreasing inflammatory conditions [52]. HT-29 Nude Mice Cell Xenograft reported to oral administration of 10 mg/kg body weight 3 times per week for 43 days. Baicalein causes harm to DNA and mistakenly reorganizes chromatin structure. Validated experiments present data demonstrating that baicalein eliminates cells by blocking the G1 phase of cellular development. The intake method for baicalein determines whether to reduce the protective protein Bcl-2 or to raise the destructive protein Bax while p53-dependent AKT activation leads to programmed cellular death to eliminate cancer cells in test subjects [53]. The monotherapy involved intraperitoneal injection of 30 mg/kg (depending upon the body weight) given for twice per week up to 4 weeks. In human colorectal carcinoma cell line (HCT116) colon cancer cells, the substance baicalein promotes cell death through apoptosis and causes cells to stop their multiplication at the S phase stage. The mechanism allows cell death through activation of two critical proteins known as caspase-3 and caspase-9. Through its ability to block NF-κB protein activity as well as activate PPARγ, it reveals anti-inflammatory capabilities and prevents cancer development [54]. Fecal matter tests examined the action of baicalein on MMP-9 and MMP-2, which enable cancer cells to infiltrate other tissues, thus preventing CRC cell translocation. A reduction in AKT pathway activity leads to this outcome, according to research [55]. In DLD-1 colon cancer cells, baicalein demonstrates two key effects by slowing cancer cell formation while reducing harmful ROS levels [56].

AKT signaling pathway and baicalein in CRC

CRC metastasis and cell invasion are dramatically inhibited by baicalein because this compound reduces MMP-9 and MMP-2 protein levels, which mediate the breakdown of the extracellular matrix during cancer metastasis. MMP-2 and MMP-9 are controlled by AKT signaling through both normal and cancer-based tissues. Baicalein exerts its inhibitory effects on this pathway by reducing AKT phosphorylation, so MMP-2 and MMP-9 suffer reduced activity. When cancer cells are blocked from activating the AKT pathway, they lose their ability to migrate or invade. The use of Transwell chamber assays showed that baicalein efficiently minimized CRC cell migration while blocking invasion. Results from prior research demonstrate that baicalein has antimetastatic action against malignancies of the liver, glioma, and both breast and tongue cancer. Clinical Practice MMP-9 and MMP-2 impact that higher expression of MMP-9 and MMP-2 is linked to aggressive CRC progression and unfavorable survival outcomes and advanced tumor stages. During CRC treatment, both proteins emerge as fundamental therapeutic targets [57-60].

Through the p38 and MAPK ERK signaling pathways, baicalein regulates both the apoptosis of cancer cells in the colon and the processes of senescence

Three vital cellular processes known as proliferation and senescence and apoptosis function through the effector pathway known as MAPK. Reconsidering senescence and cell cycle restart after oncogenic RAS interacts at a controlled speed based on information derived from MAPK signaling pathways [61,62]. Human Treg cell-directed treatment modifies T-cell aging processes through modulation of ERK1/2 signaling cascades and p38 according to scientific research [63,64]. The study explored how baicalein influences the MAPK signaling network during S phase arrest and cell apoptosis together with senescence in colon cancer cells. The expression of MAPKs ERK1/2 p38 and JNK became activated when HCT116 and SW480 colon cancer cells received baicalein and baicalin treatments as revealed by Western blot analysis. When colon cancer HCT116 and SW480 cells received baicalein and baicalin treatment, the compounds specifically activated p38 and ERK1/2 signals without affecting JNK signals while producing high levels of p38 and ERK1/2 phosphorylation in both cellular lines. Research evidence shows that baicalein and baicalin cause specific activation of MAPK p38 and ERK1/2 signaling pathways in human colon cancer cells.

Effects of baicalin on cancer cell proliferation and death

Cell cycle regulation: The role of baicalin treatment on CRC cell cycle activities along with proliferation regulation. In the cell cycle, there are four types: G0/G1, S, G2, and M. Genetic material distribution along with replication verification functions depend on crucial checkpoints (G1/S and G2/M). CRC development strongly correlates with unregulated cell cycle control checkpoints [65]. Baicalin's Action: The G2/M phase cellular arrest allows baicalin to halt cancer cell proliferation while triggering programmed cell death. Whole-cell patterns show lower expression of critical proteins Cyclin D1 in the G1 phase combined with reduced Cyclin B1 in the G2/M phase. The natural compound baicalin prevents the development of Cyclin A and CDK2 protein interactions necessary for cell transition from the S phase to the G2/M phase [66]. Stopping the Growth of CRC: Baicalin blocks cancerous cell multiplication occurring in HT-29, SW480, and HCT-116 colon cancer cells, thereby inhibiting tumor growth. The cells accumulate during the S phase because of this effect, thus blocking tumor progression. The anticancer properties of baicalin extend from its control over

repair genes hMLH1, hMSH2, and PCNA in mismatch repair-deficient CRC cells [67]. Possibility of antitumor drug use: Research suggests that baicalin should be examined as an anticancer therapy for CRC patients with microsatellite instability. Gastric cancer and cancer in postmenopausal women remain promising areas for study because baicalin shows defined interactions with cyclins and CDKs at different doses [68].

CRC cells undergo apoptosis

Changes in cell cycle control mechanisms and tumor prevention result from baicalin treatment, which reduces antiapoptotic factors Bcl-2 and Bcl-6 while promoting proapoptotic factors p53 and Bax [69]. Baicalin's impact on SW480 colon cancer cells for a 48-h treatment duration with drug concentrations ranging from low to high [70]. After baicalin treatment, SW480 cells exhibited apoptosis-related morphological changes through chromatin agglutination, nuclear fragmentation, and cell volume reduction. As the baicalin concentration elevated within the study period, researchers noted a direct dose-response pattern resulting in elevated apoptosis rates and increased cell membrane destruction. Stress-induced ROS molecules control cellular signaling molecules and trigger apoptosis and differentiation events, as well as cell proliferative and autophagic pathways. At a high concentration, baicalin leads SW620 cells to generate substantial ROS that triggers enhanced caspase-3, caspase-8, and caspase-9 activity before terminal SW620 cell death. Different occupations in protein complexes I and II accept Ncapd2 and Ncapd3 specifically. Higher levels of Ncapd2 along with Ncapd3 expression quicken the cell cycle and block apoptosis while promoting colon cancer cell survival and multiplication [71]. The Wnt signaling pathway suppression occurs through activated DKK1 and reduced miR-217 expression, which leads to battles against cancer in colon cells. Exposure to baicalin results in Notch pathway blockade in SW480 colon cells. When Notch signaling was overexpressed, research showed results that were opposite of the effects seen post-mouse Notch gene deletion, with reduced colon cancer cell proliferation, increased apoptosis, and decreased colony formation [72]. Baicalin works as an unfavorable Notch pathway regulator in human colon cancer, which leads to SW480 cell growth restrictions and cell death. In general, speaking, most of the research identified a novel mechanism for baicalin's actions against cancer, which is that it inhibits the growth of tumors by causing colon cancer cells to undergo apoptosis by decreasing the expression levels of c-Myc and onco-miRs [73].

Table 3 shows Baicalein (7-D-glucuronic acid-5,6-dihydroxyflavone) is used in TCM to prevent abortions, cool blood, reduce heat, and detoxify, acting via cell cycle regulation by blocking Cyclin A/CDK2 interactions to stabilize G1 and G2/M checkpoints. It induces cell death by lowering MMP-2/9 activities, blocking AKT phosphorylation, modulating MAPK (p38, ERK1/2), and activating caspases while tumor suppressors adjust miR-217, Notch, p53, and DKK1 levels.

ORI

An ent-kaurene diterpenoid called ORI was isolated from *R. rubescens* as shown in (Fig. 11) [74]. By targeting many oncogenic proteins primarily through Michael addition between its unsaturated ketone and the cysteines in the target proteins, ORI demonstrated a wide range of anticancer actions.

Through the inhibition of GLUT1, ORI can cause autophagy in CRC cells. Pyruvate kinase M2 (PKM2) was activated, and glycolysis was blocked by ORI, which also prevented c-Myc, GLUT1, and signal transducer and activator of transcription 3 from performing their downstream functions, ORI is a new PKM2 activator that inhibits the Warburg effect to exert anticancer effects. Studies have proven that ORI decreases Warburg effect conditions in CRC cells through gene alterations and apoptosis enhancement. The energy-related processes of ATP production and lactate synthesis, together with glucose intake, experience a dose-dependent decrease from ORI exposure. ORI the nuclear entry of PKM2 while decreasing the dimeric PKM2 amount, which results in stabilizing tetrameric PKM2 and blocking Importin-α5 from binding dimeric PKM2 [75]. The cancer development rate of CRC remains slowed down throughout live animal testing. ORI activates autophagy together with apoptosis in DLD-1 cells, thereby causing cell death while minimizing cellular growth. Autophagy and apoptosis in tumor tissues present both pathway alterations in AMPK/mTOR/ULK1 signaling and protein expression changes of autophagy-related proteins and apoptosis [76].

ORI blocks the growth of CRC cells while creating G2/M cell cycle delays and producing ROSs vital to HCT-15 and cell apoptosis 5-fluorouracil (5FU)-R/HCT-15. The cell growth rate of CRC cells slows down in a dosage-dependent manner through increased functions of the tumor suppressor pathways (p53 and Rb), which trigger the production of aging proteins (p21, p27, and p16). The anticancer effects of ORI receive additional support through its ability to modify histones as well as control gene regulation [77-79]. CRC cells undergo apoptosis and autophagy as a result of ORI activating the endoplasmic reticulum (ER) stress through TP53-mediated suppression of TCF4 activation. ORI loses its effectiveness when TP53 is removed because TCF4 expression will increase, and ER stress will decrease along with improved calcium regulation in cancer cells [80].

Studies investigated how ORI interferes with cells that have CRC

Research on ORI lasted 48 h when studying the SW620, HCT116, SW480, and LoVo CRC cell lines. ORI produced apoptosis at different chemical concentration levels while simultaneously lowering cell replication rates according to dosage. According to observations in HCT116 and LoVo cell types, ORI performed better than other analyzed drugs. The G2/M phase of cellular division stopped while caspase-3 and caspase-9 proteins became activated because cells experienced apoptosis. HT29 cells proved to be the most vulnerable type among all CRC cell lines tested in response to ORI treatment [81].

ORI is a potent anti-CRC compound that works through multiple mechanisms

Gao in 2010 revealed the histone Hyperacetylation and Gene Regulation – ORI increases histone acetylation and regulates genes such as c-Myc, p16, p21, and p27, leading to cell senescence and apoptosis. In 2011, Dr. Jin reported that AP-1 and NF-κβ Inhibition – ORI downregulates AP-1, which suppresses NF-κβ and MAPK pathways, stopping tumor growth. Gao said that the thioredoxin reductase (TrxR) inhibition ORI reduces TrxR activity, causing $H2O_2$ and glutathione depletion, making cancer cells more vulnerable. Kwan reported that the Lipid Metabolism Disruption, ORI inhibits SREBP1 and fatty acid synthase, affecting CRC cell metabolism. Yang studied the Apoptosis Induction of ORI works in a concentration-dependent manner, suppressing miR-32 and Bcl-2, while upregulating Bax, Bim, CytC, and activating caspase-3/-9, leading to cancer cell death. Chen studied as the Warburg Effect Suppression of ORI downregulates PKM2, preventing its nuclear translocation and reducing cancer cell metabolism. However, it does not affect the EGFR/ERK pathway [82].

Table 4 shows Rabdosia rubescens (Oridonin) impairs metabolism by blocking GLUT1 transport—reducing ATP synthesis, lactate production, and the Warburg effect—while keeping PKM2 active in its tetrameric form.It induces autophagy and apoptosis via AMPK/mTOR/ULK1 signaling, activates tumor suppressors (p16, p21, p27, p53, Rb) with enhanced histone acetylation, and enforces G2/M arrest while modulating BCL-2, miR-32, BAX, Bim, CytC, and caspase-3/9.

COMBINED ACTION OF BERBERINE, BAICALEIN, ORI IN CRC

(Fig. 12) shows that ORI, berberine, and baicalein treat colon cancer by inducing oxidative stress, arresting cell cycles, and suppressing key signaling pathways to inhibit survival and proliferation. This research focuses on developing an automated system that utilizes DCNN to analyze histopathological images of colon tissues [83].

DISCUSSION

Chinese medicinal herbs may be used to treat colon cancer, according to recent research. Cinnamomi Ramulus (CR), according to research

Table 3: Properties of baicalein compound and their actions

Category	Details	Reference
Source	Baicalein (7-D-glucuronic acid-5, 6-dihydroxyflavone)	[49]
Traditional Uses	Prevent abortions while cooling blood and reducing heat and removing toxic substances (TCM)	[50]
Mechanism in pathway	The mechanism of this pathway functions through cell-cycle regulation-b which prevents cyclin A from reaching CDK2 to stabilize both G1 and G2/M checkpoint stages. The anti-apoptotic mechanism functions through lower MMP-2 and MMP-9 activities and blocked protein kinase B phosphorylation while also elevating Bax and depleting Bcl-2 and activating caspase-3, -8, and -9. Through its mechanisms on MAPK (p38, extracellular signal-regulated kinase 1/2), the pathway triggers cell death and aging processes. When tumor suppressors are activated they lower miR-217 and Notch signaling levels and elevate p53 and DKK1 amounts.	[52,65,73]

MAPK: The mitogen-activated protein kinases, MMP: Matrix metallopeptidase

Table 4: Active phytoconstituents of oridonin and its mechanism

Category	Details	Reference
Source	*Rabdosia rubescens* (ent-kaurene diterpenoid: Oridonin)	[73]
Metabolic Effects	The inhibitory effect of Metabolism blocks the glucose transporter 1 transport pathway while decreasing ATP synthesis and limiting lactate production together with inhibition of the Warburg effect	[74]
Effects on PKM2	Impact on PKM2 The compound maintains tetrameric PKM2 in an active form while blocking its nuclear relocation.	[75]
Cell Death Mechanisms	Mechanisms of Cell Death cause autophagy and apoptosis through Adenosine monophosphate-activated protein kinase/the mechanistic (or mammalian) target of rapamycin/ Unc-51-like kinase 1 signaling.	[76]
Tumor Suppressor Activation	Activation stimulates p16, p21, and p27 protein expression while it both activates p53 and Rb.	[77-79]
Gene and Histone Regulation	Genes and Histones on p16, p21, and p27 and *c-Myc* genes occur through elevating histone acetylation levels.	[82]
Cell Cycle Arrest	Through cell cycle arrest cancer cells cannot divide because the pathway blocks them at the G2/M phase.	[81]
Apoptosis Pathway	Bcl-2 and miR-32 expression decreases at the same time BAX and Bim and CytC levels increase with simultaneous activation of caspase-3 and -9.	[82]

PKM2: Pyruvate kinase M2

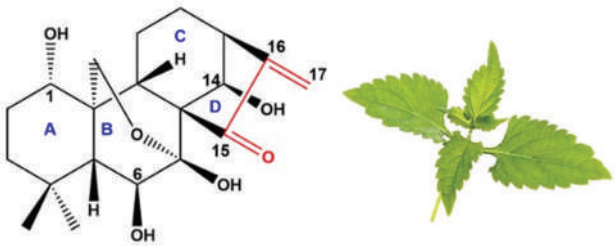

Fig. 11: *Rabdosia rubescens* oridonin

from 2022, suppresses the AKT/ERK signaling pathways and induces apoptosis to prevent the growth of cancer cells [84]. Studies conducted in 2021 also show that *Oldenlandia diffusa* and *Scutellaria barbata* preserve healthy cells while specifically targeting cancer cells, indicating that they may be useful therapeutic agents [85]. Teng-Long-Bu-Zhong-Tang has also been demonstrated to increase apoptosis, promote cellular senescence, and inhibit angiogenesis when paired with 5-FU, all of which improve the overall effectiveness of chemotherapy [86]. According to these results, Chinese medicinal herbs may be used as supplemental treatments for colon cancer; however, more clinical studies are necessary to confirm their safety and therapeutic efficacy. By 2040, it is predicted that at least 42% more people will need palliative care services in England and Wales. It is not known if introducing advanced clinical practitioners to palliative care environments is beneficial to patients and healthcare organizations [87].

FUTURE PERSPECTIVES

The pre-clinical results of berberine, baicalein, and ORI in colon cancer models, subsequent research should focus on evaluating their efficacy and safety in clinical trials to validate their potential as adjunctive or primary treatments for colon cancer. Investigation of the synergistic effects between these plant-derived compounds and conventional chemotherapy agents, such as 5-FU or oxaliplatin, could potentially enhance treatment effectiveness while mitigating adverse effects. Furthermore, a more comprehensive exploration of their molecular mechanisms, including key signaling pathways such as EGFR and AMPK/mTOR, is warranted, utilizing comprehensive group approaches to identify additional molecular targets. Addressing challenges related to the bioavailability and pharmacokinetics of these compounds is essential, potentially through the development of novel delivery systems or co-administration strategies. Elucidation of how these compounds influence the tumor microenvironment, including immune modulation, could reveal new avenues for immunotherapy. Moreover, integration of genetic and epigenetic profiling to develop personalized treatment strategies, as well as exploration of their role in chemoprevention, particularly for high-risk populations, will be critical in optimizing their clinical application and broadening their impact in CRC therapy.

CONCLUSION

A successful therapeutic approach against CRC might result from using the combined treatment of ORI and berberine with baicalein. The compound ORI disrupts glycolytic activity along with promoting apoptosis and autophagy through activation of AMPK/mTOR/ULK1 signaling. The combination of these factors makes ORI better at fighting cancer while adjusting ROS and JNK/c-Jun pathways. Cancer cell proliferation remains inhibited while apoptosis activates and cell cycle arrest develops in CRC cells because of berberine intervention. The compound disrupts cell proliferation channels that involve EGFR while simultaneously blocking COX-2 enzyme activity to prevent cancer cell migration. As an anti-cancer agent, baicalein performs three functions, including inhibition of cell proliferation, inducing programmed cell death, and blocking

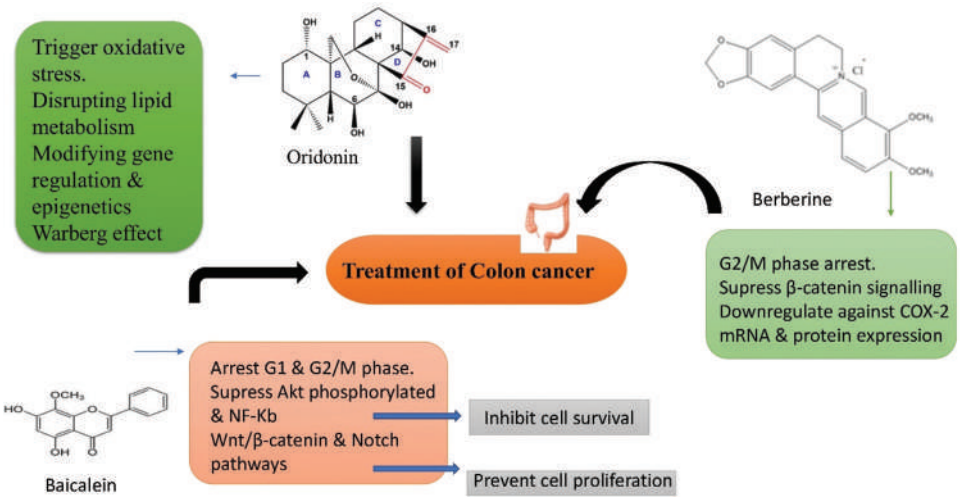

Fig. 12: Action of berberine, baicalein, and oridonin in colorectal cancer

cancer cell mobility. The substance prevents the development of EGFR along with carcinogenic proteins through its regulation of signaling pathways such as NF-kB and PI3K/AKT. The compounds affect various stages of CRC evolution, from metabolic processes to cell cycle control to apoptosis and inflammation, thus enabling a substance-based multi-target therapeutic approach. Additional investigations, together with clinical trials, must be performed to properly assess CRC treatment outcomes using combined treatments.

DATA AVAILABILITY

No empirical data were utilized in the research outlined within this article.

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CRedIT AUTHORSHIP CONTRIBUTION STATEMENT

Suruthi Ramamoorthy: Writing-original draft, data curation, resources, conceptualization. Jubilee Ramasamy: Writing-review and editing, Writing- original draft, Supervision, Data curation, Conceptualization. Gopinath Sambasivam: Writing - Data curation Review and editing.

DECLARATION OF COMPETING INTEREST

The authors hereby affirm that they possess no recognized competing financial interests or personal relationships that might be perceived to have influenced the work presented in this manuscript.

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