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Juxtacrine and Paracrine Events in the Colorectal Carcinogenesis with their Herbal Remedies: A Review

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Abstract

Colorectal cancer is one of the lethal types of malignancies leading to a high mortality rate globally due to various risk factors involving inherited genetic disorders which includes FAP (Familial Adenomatous Polypsis), HNPCC/Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer), Turcots syndrome, Peutz jeghers syndrome and some inflammatory bowel diseases. On such occasions, the development of tumor comprises five different stages that are progressed via multiple signalling pathways. The molecular events for the cancer progression incorporate two major types of cell signals, i.e., Juxtacrine and Paracrine where cell-cell or cell- extracellular matrix communicates to produce signals. The former event implies the Notch and Hippo signalling pathways. The latter entails the cascade cell communication process such as Wnt/ β -Catenin, MAPK (mitogen-activated protein kinase), TGF-β/SMAD (Transforming growth factor beta), PI3K/AKT (Phosphoinositol 3-kinase), TP-53 (Tumor protein 53), VEGF/VEGFR (Vascular endothelial growth factor), JAK/STAT (Janus kinase/Signal transducer and activator of transcription), Nrf2/KEAP1 (Kelch-like ECH-associated protein 1), SHH (Hedgehog), cMET/HGF (Hepatocyte growth factor), resulting in metastatic cancer. Timely identification of the resultant and appropriate treatments such as cytotoxic medicines, radiation, chemotherapy, and surgery can prevent severe cancer causes. Recently, the emergence of herbal/ natural treatments paves the way for cancer control without any significant side effects over usual treatments. Among other natural remedies, Traditional Chinese medicine is considered to be an ancient method of herbal treatment for the progression of cancer. Thus, this article aims to provide an overview of the cell communication process and to elicit the herbal remedies that help in colorectal cancer therapy.

Keywords: Cell signal, Colorectal carcinogenesis, Herbal remedies, Juxtacrine, Paracrine.

1.Introduction

Cancer is an uncontrolled growth of cells or mass of tissues leading to the formation of tumor/neoplasm. These cells are differentiated into benign and malignant based on the rate of cell proliferation.[1] Various risk factors can potentially alter the normal cells to proliferate, i.e., radiation or chemical exposure, genetics, dietary habits, environmental changes, and idiopathic causes, leading to the development of malignant cells. Based on the cells or tissue origin, cancers are classified into various types (e.g., lung cancer, breast cancer, colorectal cancer, urothelial cancer, etc.).[2] This review focuses on colorectal cancer, which originates from the colon/rectal site tissue lining.

Colorectal cancer (CRC) is the third most common type of malignancies, also known as colon/ rectal/ bowel cancer[3], and it is the second leading cause of mortality related to carcinogenesis.[4] According to the WHO report, 1.93 million cases of colorectal cancer were recorded in the year 2020, and the number of deaths was accounted to be 935000 in the same year.[5] In 2030, it is anticipated to increase by 60.0% (i.e., new cases-2.2 million and deaths-1.1 million).[6] The highest prevalence is seen in women aged between 60-75 than in men . Initially, risk development is observed in the epithelial lining of the colon.[7] Colorectal carcinogenesis is considered if cancer in the colon lining spreads 6 inches down and reaches the rectum.

This process involves five different stages ranging from stage 0- stage 4, which also contains subtypes defining the progressive development of cancer from the initial stage (adenomatous polyps) to the late developed stage (metastatic), resulting in death.[8] These stages imply various cellular events, i.e., Two major communications: **juxtacrine** (cell-cell or cell-EC matrix signaling occurs in close contact cell) and **paracrine** (cell-cell signaling, altering the other occurs with the relative contact cells).The signal interchange between distinct cells and dysregulation in many illnesses is essential for cell development and function. The process for signal transduction begins with the paracrine or the juxtacrine factor, which causes the cell membrane receptor to change shape.[9] This critical cell communication encompasses various signalling pathways, which helps in the formation of metastatic cancer. The comprised paths are genetically/epigenetically altered or mutated in the carcinogenesis process. The genetic alteration includes mutation of the APC gene, HNPCC (Hereditary Non-Polyposis Colorectal Cancer), Turcot's syndrome, and Peutz Jeghers Syndrome.[10] The mutagenicity is diagnosed by medical imaging, colonoscopy or sigmoidoscopy, pathological or histopathological studies, and radiology. More than half of the cases are occurred due to the modified lifestyle factor.[11] It is suggested that early detection can prevent the causes, and one-fourth of the cases can be cured. It is controlled by preliminary screening and treating it with appropriate medicines and supplements. The treatment of CRC is based on the different stages of cell proliferation.[12] As detected in the primary stage, surgery removes the polyps from the colon's lining. Other treatments are palliative care, chemotherapy, radiation therapy, immunotherapy, and natural remedies. Conventional therapies like chemotherapy and surgery are associated with the main problems such as drug-drug interaction, adverse effects, drug resistance, cytotoxicity, complications, and discomforts (Bleeding, deep vein thrombosis, nausea, pulmonary embolism, etc.). [13]

Many efficient lead compounds have been found through diverse and complex natural ingredients to discover new products to prevent such issues. In the treatment of cancer, there is a long history of using plants[14] ; however, most claims on the effectiveness of this treatment are skeptical. These drugs are less toxic and well-tolerated, enhancing patients' treatment results and improving their quality of life. [15]

2. Juxtacrine Pathways

The ligand and receptor of adjacent cells forming a stable signalling complex is juxtacrine signalling. In this, proteins from the induction cell interact with the protein receptor of adjoining reacting cells in multicellular organisms whereas, in single-cell organisms like bacteria, Juxtacrine communication refers to membrane-contact interactions.[16] Based on this, three sorts of interactions exist, they are:

1. The one cell protein binds on the neighbouring cell's receptor
2. A cell receptor binds to a ligand with a cell-secret extracellular matrix.
3. Small conduits directly convey the signal into a neighbouring cell's cytoplasm from one cell's cytoplasm.[17]

Some growth factors, cytokine, and chemical cell signals were shown to have juxtacrine signalling that plays a significant role in the immune response. It also has a crucial role in developing heart and neural function in specific. Among various signaling pathways in CRC, the major **NOTCH** and **HIPPO** signaling come under the juxtacrine type of cell communication. Any dysregulation /mutation induces the uncontrolled growth of epithelial cells and reduces the apoptotic impact.[16]

2.1 Notch Signalling Pathway

Various investigations in patients with CRC have suggested that the Notch pathway is involved in CRC development, and several mechanisms have been presented to demonstrate this function.[18] It has become evident that Notch signaling regulates various cell processes linked to proliferation, differentiation, and death that occur intracellularly. Generally, this pathway comprises four notch receptors (NOTCH 1-4), five ligands such as delta-like[DLL-1,3&4] and Jagged [JAG 1-2], and multiple targeted downstream genes (Hes-1, p21, Deltex). These receptors of the notch contain two domains [Notch Extracellular Domain (NECD) & Notch Intracellular Domain (NICD)] and the certain component of transmembrane. Initially, signal transduction is triggered by a cross ligand contact between one cell and the Notch transmembrane receiver present in the neighboring cell. Through the ubiquitination process, ligands of the DLL/ Jagged protein of the transmitting cell get activated.[19] These ligands subsequently attach to the receptor of an extracellular domain where S2 cleavage (proteolytic cleavage) occurs by the enzyme ADAM protease and disintegrin, which leads to its dissociation. Sequentially, S3 cleavage by the γ- secretase enzyme results in the release of NICD from the transmembrane domain to the cytoplasmic matrix. The released intracellular domain gets attached and activates hairless recombining binding protein suppressors, such as CSL, forming a complex with co-activators(MAML, p300) by replacing the existing co-repressors. The resultant complex swifts to the nucleus, where it activates the transcription factors/oncogenes. The overexpression of notch ligand, receptors, and downstream genes leads to complicated carcinogenesis in patients with CRC. Their expression is relatively higher in the early stage than in the late developed stage. Cell cycle and apoptotic target gene regulation promote CRC severity via a notch pathway. So the suppression of this pathway may be one of the therapeutic benefits of colorectal cancer.

2.2 Hippo Signaling Pathway

The hippo signaling pathway was regarded as one of the most important signals of carcinogenesis and helps in cell regulation, morphology, migration, survival, organ size, homeostasis of tissue, and proliferation. Also, it can act as an inhibitor for various tumor developing components through MST (macrophage stimulating),TAZ(taffazin),YAP-1 (Yes-associated protein 1), LATS (large tumor suppressor kinase), TEAD (transcriptional enhancer associated domain) and fat storage-inducing transmembrane protein.[18] Primarily, MST is enhanced with the FAT transmembrane protein and increases the LATS to YAP phosphorylation, inhibiting YAP from translocating from the cytoplasm to the nucleus. YAP-1 is the main transcriptional regulator, which in association with PDZ binding domain taffazin tune the pathway. The phosphorylation prevents the complex YAP/TAZ in the nucleus from interacting with TEAD, which results in oncogene inactivation. According to the previous studies, three protein elements are represented in mammals: Ste 2 like kinase(1&2) and large tumor suppressor kinase (1&2). [20] The phosphorylation of mammalian proteins occurs simultaneously, which phosphorylates the YAP/TAZ complex in the nucleus and removes it to the cytoplasm. Upon ubiquitin-mediated protein, the complex in the cytoplasm gets degraded. In CRC, as mentioned earlier, the process is suppressed, and there will be a high level of YAP, resulting in the proliferation of cancer cells. Thus, mutation of this path can interfere with the other signaling pathways that cascade this process. Decreasing the overexpression/level of YAP can be a better therapeutic effect.

3. Paracrine Pathways

Paracrine signaling is one of the types of cell communication in which cells next to one other interact by releasing chemical messengers (Ligands that can spread over cellular space).[21] These communications occur over relatively short-distance cells. They enable cells to coordinate activity locally with their

neighbors.[22] They are often largely dependent on extracellular contexts and give fine-level possibilities. The molecules conveying signals are paracrine factors, which only create a local effect and an anti-endocrine effect. One of the examples of the paracrine factor is the FGF family (Fibroblast growing factor).[23] Various molecular events that come under this cellular communication are Wnt/β-catenin signaling pathway, EGFR/MAPK signaling pathway, PI3K/AKT signaling pathway, VEGF/VEGFR pathway, JAK/STAT signaling pathway, TGF-β signaling pathway, SHH signaling pathway, p53 signaling pathway, KEAP1/Nrf2 signaling pathway, and HGF/cMET pathway.

3.1 Wnt/ β -Catenin Signaling Pathway

The Wnt signaling pathways are a collection of signals that begin with proteins transmitting a signal by receptors of the cell surface.[24] It performs diverse biological activities and stimulates the growth and development of intestinal epithelial crypt in particular. They are of two types: canonical (β- dependent) and non-canonical (β-independent). The canonical pathway maintains the crypt stem cell compartment in normal cells; thus, it plays additional roles in cell physiology and pathology. Any alteration/mutation in this pathway leads to colorectal carcinogenesis. Cell surface receptors consist of LDL-LRP receptor complexes and frizzled (Fz) receptors. Alongside this, there is a multiple protein intra-cellular complex. Axin, β-catenin, disheveled (Dsh), the glycogen synthase kinase-3β (GSK-3), and the APC are present. APC(tumor suppressor gene) is a key negative regulator of β-catenin. In the resting cell, this APC protein normally binds to and promotes the degradation of β-catenin. But when the ligand occupies the surface receptors/ cell is mutated, WNT is stimulated by signaling that prevents the destruction complex formation.[25] The absence of destruction complex stabilizes and accumulates β-catenin. It translocates from the cytoplasm to the nucleus, where the transcription complex and transcription genes are activated, i.e., β-catenin/TCF, MYC, cyclin D1. The activation results in the proliferation of colonic epithelial cells. The wnt/β-catenin signal pathway is critical in the migration and invasion of tumor cells during metastatic CRC development.

3.2 EGFR/MAPK Signaling Pathway

The MAPK pathway is involved in several biological activities such as cell development, multiplication, and cell survival. EGFR, the membrane-bounded tyrosine kinase receptor present on the cell surface, plays an active part in the genesis and progression of various malignancies.[26] The autophosphorylation on the intercellular domain of the transmembrane protein of the tyrosine residue occurs when the EGF ligand occupies the surface receptors. This phosphorylation offers a cellular sequence of events, i.e., the Grb-2 adapter molecule connects through its SH2 domain with the phosphorylated tyrosine, followed by contact with the son of sevenless (SOS) via the Grb-2 SH3 domain. SOS, an exchange factor of Guanine Nucleotide, permits GTP to be converted to a RAS molecule from GDP to be activated. Through the process of phosphorylation, the activated SOS initiates kinase pathways like MAPK/ERK (extracellular signal-regulated kinase), MAPKK-MEK (mitogen-activated protein kinase), MAPKKK-Raf (mitogen-activated protein kinase kinase kinase). MAPK may control the nuclear substrate directly, and ERK influences cellular processes, including cell proliferation and cell survival, by addressing the substrates of the cytoplasm or nucleus.[27] The dysregulation of this route leads to survival, growth, neoplastic cell metastasis, angiogenesis, and Kras mutation. In CRC, the cells show abnormal regulations, promotion, increasing copy numbers, and upregulation of EGFR, supporting the activation of MAPK.[26,27] So the inhibition of the mutated KRAS gene has been considered to be a better therapeutic effect.

3.3 PI3K/AKT Signaling Pathway

PI3K is one of the pathways triggered by EGFR, which resembles glucose metabolism. Akt, serine/threonine kinase protein, modulates the effects of PI3K on tumor development and tumor progression.[28] Akt is, therefore, a downstream PI3K effector. In this PI3K initiates phosphorylation of PIP2 (phosphatidylinositol-4,5-bisphosphate) to PIP3 (phosphatidylinositol-3,4,5-trisphosphate) that facilitates cascade intracellular signalling by Akt phosphorylation.The PIP3 stimulates AKT, leading to cell proliferation and cell survival, where AKT controls downstream targets like mTOR that stimulate angiogenesis, translation of protein, growth, and metabolism.[29] The PI3K pathway leads to cancer cell proliferation and transformation and mediates proteins known in human malignancies as phosphoinositol phosphatases, whereas in normal cells, PIP3 degrades, and phosphoinositol phosphatases(PTEN, PIPP (INPP5J), and INPP4B) terminate its signal.[30] About 70% of the CRC has been reported with p-Akt overexpression and impairment of PTEN expression. Developing targeted therapy produces a significant effect in the treatment of tumorogenesis.

3.4 VEGF/VEGFR Pathway

The VEGF pathway is closely related to angiogenesis, which is essential for developing the tumor and metastasis. The VEGF protein family includes five proteins, namely VEGF-A, B, C, D, and placental growth factor (PIGF), which bind to three types of tyrosine kinase receptors such as VEGFR-(1,2,3).[31] In addition to this, there are two non-kinase receptors they are neuropilin (NP-1,2). These proteins show diverse effects when binds to the receptors where it contributes primarily to angiogenesis. Initially, the binding of VEGF ligands to VEGFRs starts the signaling cascade, which further activates many downstream processes. Each kinase receptor has specific functions such that VEGFR-1 in the inflammatory, tumor and, endothelial cells encourage cell differentiation and migration, VEGFR-2 in the lymphatic epithelial and blood promotes cell growth and, VEGFR-3 in lymphatic epithelial cells regulates cell proliferation, migration, survival, and differentiation.[31] It is evident that the VEGFR activity and VEGF levels are higher in patients with colorectal cancer. The VEGF/VEGFR complex's proangiogenic role is crucial at the initial site of tumor progression and migration, as well as at the metastatic site for new blood vessel formation to support cancer proliferation and cell survival.[32] Anti-VEGF or anti-VEGFR therapy may reduce tumor production and spread by targeting this complex.

3.5 JAK/STAT Signaling Pathway

The JAKs/STAT pathway has been implicated in a variety of oncogenic and cancer-related events, including cell metastasis, proliferation, inflammation, invasion, and differentiation. It consists of four types of Janus kinase proteins (JAK1, JAK2, JAK3, and TYK2) that interact with cytokine receptors associated with signal transducer and activator of transcription (STAT) protein. The activation of JAKs is triggered when cytokine ligands or growth factors attach to receptors on the cell surface.[33] The active JAKs then cause STAT to be phosphorylated and dimerized, allowing it to translocate into the nucleus and increase the transcription of many downstream genes. The overexpression of this pathway leads to malignant CRC traits. According to research, the level of phosphorylated STAT in colorectal adenocarcinomas is substantially higher than in carcinoma. Unlike normal epithelium cells, the adapted CRC cells have frequent activation of STAT.[34] Thus, it is clear that this pathway involves the progression of CRC, and the development of a targeted molecule (JAK inhibitors which bind to JAK proteins and prevent them from phosphorylating, ultimately stopping their function) would help in the treatment of CRC.

3.6 TGF-β Signaling Pathway

TGF- β signaling pathway is otherwise known as the SMAD pathway which, plays a role in cell differentiation, proliferation, apoptosis, migration, and adhesion, among other biological processes. TGF-R I and TGF-R II are the two membrane receptors positioned upstream of the TGF- β /Smad signaling cascade along with Smad proteins (Smad2,3). The signal transmission starts when TGF- β ligands connect to type II TGF- β receptors.[35] The initiation of the downstream regulation is when ligand binding to type II receptors and activates it. The active receptors then stimulate Smad2/3 dimer phosphorylation, allowing the Smad2/3 dimers to detach from the receptors and form the Smad2/3/4 complex with Smad4. The complex then migrates into the nucleus to influence the transcription process. In the early stage, TGF-β is known to act as a tumor suppressor, usually controlling cell division and the death of colon epithelial cells. In contrast, in the later stage, TGF expression increases and impacts epithelial-mesenchymal transition (EMT), increasing invasion and cell migration and suppressing the normal cellular immune response.[36] Therefore the development of pharmacotherapy to stop the mutation of Smad assists in the betterment of CRC.

3.7 SHH Signaling Pathway

The SHH signaling system is one of the paracrine pathways required for epithelial cell regeneration and differentiation. The HH family is a collection of proteins involved in various biological processes that play an essential role in controlling embryonic development, modulating proliferation, and determining cellular destiny.[37] The secretory cells of the endoplasmic reticulum generate hedgehog (Hh) ligands released through the dispatch (membrane protein) and subsequently bind to the Ptc (patched)protein in the neighbor cell that inhibits the protein functions. Due to this inhibition, Smo protein in the intestinal cilia gets activated. Smo is responsible for the activation of transcriptional factors such as Gli proteins (Gli-1,2,3). Primarily, Gli-2 is activated that phosphorylates the Gli-1 factor, which translocates into the nucleus and acts on SHH genes. Consequently, Smo inhibits the functions of the Gli-3 factor.[38] Hence the patient with CRC is recorded with increased protein levels and transcriptional factors [39], and suppression of this process aid colorectal carcinogenesis.

3.8 P53 Signaling Pathway

p53 is a tumor suppressor gene that is one of the most altered genes in all types of carcinoma. In general, the p53 protein is activated in response to tumorigenic stress and DNA damage via its upstream components.[40] Depending on the level of DNA damage, the activated protein leads to cell cycle arrest, repair, or cellular death. This gene can also produce an E-3 ubiquitin ligase (mouse double minute 2 homolog (MDM-2)), a p53 negative regulator that regulates the level of cell p53 through the ubiquitination process.[41] Dysregulation in the pathway results in tumor formation with the disappearance of apoptotic activity and genetic mutation, i.e., misreading the p19 gene, enhances transcription, and inhibits ubiquitin ligase function that fails to maintain the p53 level in the cell.[41] In CRC, one-third of the tumor cases occur due to the p53 mutation. Therefore the prevention of this mutation can reduce the chances of CRC.

3.9 KEAP1/Nrf2 Signaling Pathway

The NFE2L2 gene encodes a transcription factor called nuclear factor erythroid 2-related factor, which takes place in several signaling pathways. In CRC, the oxidative stress produced by reactive oxygen species cause fibrosis, cell damage, etc. promotes cancer progression.[42] It also recognizes the target genes with

antioxidant response elements, and Keap1 (Kelch-like ECH-associated protein 1) keeps Nrf2 in the cytoplasm. This protein links Nrf2 and E3 ubiquitin ligase complex that undergoes ubiquitination and is finally degraded by the proteasome.[43] Under certain circumstances, the stimulation of antioxidant elements in the target gene makes Nrf2 detach from the Keap1 and translocates in the nucleus where Nrf2 dimers and interacts with tiny musculoaponeurotic fibrosarcoma (Maf) proteins, causing Nrf2 to bind to antioxidant response elements and trigger transcriptional activation of target genes .[44] Thus the targeted drug development of this pathway provides a better treatment regimen for CRC.

3.10 cMET/HGF Pathway

The HGF signaling pathway and receptors are required for cell invasion, survival, proliferation and play a vital role in organ protection and treatment resistance. cMET is a tyrosine kinase receptor that binds to the HGF ligand, undergoes phosphorylation and homodimerization, and produces a significant effect.[45] As soon as the receptor gets occupied, it is activated and initiates various downstream signaling pathways(JAK-STAT, PI3K-AKT, etc.). In CRC, the HGF level in the serum is high, and there is an overexpression of MET leading to gene mutation, metastasis, and proliferation. Another factor, such as the MACC1 (metastasis-associated in colon cancer 1) gene, has been found to influence metastatic carcinogenesis in recent times. HGF triggers MACC1 to translocate into the nucleus from the cytoplasm and promotes increased expression of MET when it binds to it.[46] This overexpression leads to the interaction with various signaling events and produces a critical cancerous effect. Inhibition of the significant receptors can help in the therapy of CRC.

4. Herbal Remedies for Colorectal Carcinogenesis

Early detection and treatment of cancer improve an individual's chances of survival elsewhere over the world. Among various therapies like chemotherapy, surgery, radiotherapy, etc., phytotherapy, also called phytomedicine [47], is one of the therapeutic methods where plant extract mixtures are used to treat CRC. Medicinal herbs can help the body protect, control, and cure itself, supporting physical, mental, and emotional health. There were several herbal treatments available such that they are grouped into Chinese and Western herbal medicines, which are the two most popular types of herbal medicine utilized in the United Kingdom, and Ayurvedic medicine or Tibetan are two less popular kinds used in India. Western herbal medicines involve the use of herbs grown from American and European countries. Chinese herbal medication uses Chinese herbs to treat ailments.[49] Out of two types, Chinese medicines are used widely for cancer treatment. They are also known as TCM (Traditional Chinese Medicine) [48], the most used complementary and alternative therapy. It has been found to lessen radiation and chemotherapy's toxicity and adverse effects, increase immunological function, decrease postoperative metastasis and recurrence, and alleviate cancer symptoms. Furthermore, oral CHM can improve quality of life, increase survival rates, and improve tumor response in the short term.[49]

In the treatment of advanced-stage colorectal malignancies, herbal medications are commonly used. They are administered usually by prescribing a single or complex recipe, including various herbs.[51] There were no serious adverse effects recorded when compared to the standard conventional treatment. As a result of the beneficial effects that herbal remedies have demonstrated, their potential application in cancer prevention and therapy has been widely recommended.

Table 1. Some of the herbs involved in the treatment of cancer[50]

S.NO	HERBAL MEDICINES	LATIN NAME
1	Astragalus	*Astragalus propinquus*
2	Burdock Root	*Arctium lappa*
3	Dong Quai	*Angelica sinensis*
4	Hypericin	*Hypericum perforatum*
5	Pipewort flower	*Flos eriocauli*
6	Ginger	*Zingiber officinale*
7	Turmeric	*Curcuma longa*
8	Catclaw Buttercup Root	*Ranunculus ternatus*
9	coix seed	*Semen coicis*
10	spikemosses	*Selaginella doederleinii hieron*
11	Chinese senna	*Semen cassia*
12	cocklebur	*Xanthium fructus*
13	costus	*Radix aucklandiae*
14	magnolia-bark	*Magnolia officinalis*
15	Peony root	*Paeoniae radix rubra*
16	pokeroot	*Phytolaccae radix*
17	duckweed	*Portulaca oleracea*
18	Tuber fleece flower	*Fallopia multifora*
19	Goji	*Lycii fructus*
20	Essiac Tea	-

5. Conclusion

Colorectal cancer is a diverse and multifactorial complex[52] disease comprising several signaling pathways leading to the evolution of five different stages. In most cases, each cancer stage produces different progressions starting from the adenoma to the metastasis mediated by multiple signaling pathways. Several hereditary factors can also influence CRC, which covers 1% of the total affected results. Based on this, we sought to outline the two critical cellular events (Juxtacrine and Paracrine) and their mechanisms involved in cancer progression and numerous signal transduction and cell death disorders. In addition to that, we summarized the existing natural/ herbal medicines used to treat the CRC better without any significant side effects. In CRC, signaling system dysregulation promotes cell proliferation and migration while limiting cell differentiation and apoptosis. It is suggested that these mutations be identified and evaluated. So the development of targeted therapy could be the best choice for the treatment regimen. In such a case, targeted herbal remedies would be a better option as they comprise fewer side effects than the current conventional treatment. Despite this information, we need to focus on the in-depth concepts of the dysregulated pathways by concentrating on cellular cross-talk to develop more efficient therapeutic approaches, which will help us develop the targeted herbal remedies.

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