Research Progress on the Role of Plant-Derived Natural Molecules in Inhibiting the Metastasis of Colorectal Cancer Cells

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Abstract: Colorectal cancer is a common and deadly cancer, with metastasis being the primary cause of its lethality. Traditional chemotherapy drugs are highly toxic to normal cells, necessitating the development of new therapies. Plant-derived natural molecules have shown significant potential in preventing and treating colorectal cancer metastasis, offering advantages over chemotherapy, such as lower toxicity, fewer side effects, and higher efficacy. Further research is crucial to identify novel natural compounds for treating colorectal cancer metastasis. While extensive reviews exist on plant-based drugs for cancer, few focus on colorectal cancer metastasis. This review highlights several promising plant-derived compounds with potential clinical applications.

***Keywords*:** colorectal cancer, metastasis, plant-derived molecules, chemotherapy, clinical applications

1. Introduction

Colorectal cancer (CRC) is one of the most common and deadly cancers in the digestive system, with over 2 million diagnoses and approximately 900,000 deaths worldwide in 2018[1]. Despite advances in treatment, metastasis remains a major cause of death, making the development of effective anti-metastatic drugs crucial[2]. The pathogenesis of CRC involves two primary mechanisms of genetic instability: chromosomal instability (CIN), which accounts for about 84% of cases, and microsatellite instability (MSI), which accounts for 13-16%. The molecular mechanisms of CRC metastasis are complex, involving key factors like proteolytic enzymes, adhesion molecules, and cell survival molecules. Epithelial-mesenchymal transition (EMT) plays a critical role in metastasis, and inhibiting EMT can effectively prevent it. Current treatments have limited efficacy in targeting these pathways, highlighting the need for new drug development.

2. Polyphenols

Polyphenols, including curcuminoids, flavonoids, and stilbenes, exhibit significant potential in inhibiting colorectal cancer (CRC) metastasis. Curcumin, a key curcuminoid, regulates gene expression, suppressing miR-21 and enhancing tumor suppressor Pdcd4, while improving the effectiveness of 5-fluorouracil and FOLFOX chemotherapy[3]. Calebin A, a curcumin derivative, sensitizes CRC cells to chemotherapy through the p65-NF-κB pathway[4]. Flavonoids like euxanthone, silibinin, and quercetin target multiple pathways, with euxanthone inhibiting CRC metastasis via the CIP2A/PP2A pathway and silibinin inducing apoptosis via mitochondrial and extrinsic death receptor pathways. Quercetin, though limited by absorption issues, shows promise in inhibiting CRC metastasis, particularly in the lungs. Stilbenes, particularly resveratrol, reverse EMT, suppress Wnt/β-catenin signaling, and inhibit FAK, reducing CRC invasion and metastasis. THSG, pinosylvin, and pterostilbene, similar to resveratrol, further inhibit CRC cell migration, invasion, and metastasis through NF-κB and PI3K/Akt pathways. Together, these polyphenols demonstrate multi-target anticancer properties, highlighting their potential in CRC treatment.

3. Alkaloid

Alkaloids are natural nitrogenous compounds with complex ring structures, and they are increasingly studied for their anti-cancer properties. Indole, isoquinoline, pyridine derivatives, and terpenes are key alkaloid groups with anti-metastatic effects in colorectal cancer (CRC). Evodiamine, an indole alkaloid from Evodiae fructus, inhibits CRC cell migration and invasion by increasing Sirt1 and suppressing NF-κB-p65. However, its poor solubility limits its clinical use, prompting research into targeted nano-carriers. Isoquinoline alkaloids like berberine and coptisine show strong anti-cancer activity. Berberine activates AMPK, reduces MMP expression, and inhibits migration, making it a promising multi-target treatment. Coptisine induces apoptosis and cell cycle arrest in CRC cells, though further research is needed. Jatrorrhizine blocks CRC metastasis by inhibiting the Wnt/β-catenin pathway and EMT. Pyridine derivatives such as matrine and oxymatrine also show promise in CRC treatment. Matrine inhibits CRC invasion and migration by reducing MMP expression, while oxymatrine prevents metastasis by inhibiting PKM2 and GLUT1. Piperine, from pepper, suppresses CRC cell migration

through the STAT3/Snail-mediated EMT pathway. Paclitaxel, a terpene alkaloid, stabilizes microtubules, inhibiting CRC cell migration and metastasis[5-6]. When combined with oxaliplatin or miR-193a, it enhances treatment efficacy by inducing apoptosis. Although alkaloids show great promise, further research is needed to clarify their mechanisms and ensure their clinical safety for CRC treatment.

4. Steroids

Steroids are naturally occurring compounds with a cyclopentano-perhydrophenanthrene ring structure. Plant-derived steroids, such as solasodine and Paris Saponin VII (PSVII), show significant potential in inhibiting colorectal cancer (CRC) metastasis[7-8]. Solasodine, from Solanum nigrum L., suppresses CRC cell proliferation and migration by modulating matrix proteases and activating the AKT/GSK-3β/β-catenin apoptosis pathway. However, its poor solubility limits clinical use, prompting research into nano-carriers. PSVII, a steroidal saponin from Trillium tschonoskii, inhibits CRC cell growth and induces apoptosis by affecting the MAPK and Akt/GSK-3β pathways. It also reduces tumor size in xenograft models and suppresses metastasis by downregulating MMP-2 and MMP-9. Cardiac glycoside convallatoxin (CNT) from Adonis amurensis inhibits HCT116 cell growth and induces apoptosis through the JAK2/STAT3 and mTOR/STAT3 pathways. Peiminine, a steroidal alkaloid from Fritillaria thunbergii, suppresses CRC metastasis by modulating EMT-related markers like E-cadherin and N-cadherin, though its exact mechanism remains unclear. While plant steroids show promise, further research is needed to clarify their mechanisms and develop effective treatments for CRC metastasis.

5. Quinonoids

Quinonoids, including benzoquinones, naphthoquinones, phenanthraquinones, and anthraquinones, are natural compounds with significant anticancer activity. Thymoquinone (TQ), a benzoquinone from black cumin seeds, inhibits CRC metastasis by suppressing NF-κB and enhancing JNK/p38 activities, showing promise for CPT-11-resistant cases. Shikonin, a naphthoquinone from Lithospermum erythrorhizon, reduces CRC cell proliferation and invasion by upregulating SIRT2. Tanshinone II-A, a phenanthraquinone from Salvia miltiorrhiza, inhibits CRC invasion, metastasis, and angiogenesis by downregulating MMPs and HIF-1α, and regulating EMT through the β-arrestin1/β-catenin pathway[9-10]. β-lapachone, an anthraquinone from Tabebuia avellanedae, reduces CRC migration and lung metastasis by inhibiting MMPs. Cassialoin, another anthraquinone, suppresses tumor growth and metastasis by targeting angiogenesis and enhancing immune responses. Emodin derivatives, including chrysophanol and rhein, inhibit CRC cell migration, regulate EMT, and promote apoptosis. These quinonoids exhibit potent anti-metastatic effects, though further research is needed to fully understand their mechanisms and optimize their clinical use.

6. Triterpenoids

Triterpenoids, found widely in nature, especially in dicotyledonous plants, are known for their anticancer properties, particularly in inhibiting colorectal cancer (CRC) metastasis. Betulin and betulinic acid reduce CRC cell metastasis by inducing apoptosis and cell cycle arrest, with betulin activating AMPK and inhibiting the PI3K/Akt/mTOR pathway. Boswellic acid from Boswellia serrata inhibits CRC tumor growth and metastasis by downregulating NF-κB and reducing pro-angiogenic markers. Celastrol, from Tripterygium wilfordii, suppresses CRC metastasis by blocking the CXCR4/CXCL12 pathway, while cucurbitacin I enhances chemotherapy sensitivity by downregulating Phospho-Stat3 and MMP-9. Ginsenosides, including Rg3, Rd, Rh2, and Rb2, inhibit CRC metastasis through reduced cell migration, invasion, and angiogenesis, while promoting anti-tumor immunity and chemotherapy sensitivity. Ursolic acid, found in many traditional Chinese herbs, inhibits CRC growth and metastasis by blocking angiogenesis, NF-κB activation, and EMT[11]. While these triterpenoids show promising potential, further research is needed to fully understand their mechanisms and clinical applications.

7. Phenylpropanoids

Phenylpropanoids, including rosmarinic acid and esculetin, show significant anti-metastatic potential in colorectal cancer (CRC). Rosmarinic acid, from Prunella vulgaris, inhibits CRC cell migration, adhesion, and invasion by reducing MMP-2 and MMP-9 activity, likely through the extracellular signal-regulated kinase pathway[12-13]. In animal models, it significantly reduced tumor weight and pulmonary nodules, demonstrating strong anti-metastatic effects. Esculetin, from Cortex Fraxini, suppresses CRC metastasis by inhibiting Wnt signaling, increasing E-cadherin expression, and reducing β-catenin and Axin2 levels. It significantly reduced tumor volume and weight in vivo without toxicity, highlighting its therapeutic potential. Both compounds show promise for preventing CRC metastasis.

8. Polysaccharides

Polysaccharides, large molecules made of monosaccharides, exhibit various biological activities, including anticancer effects. Modified apple polysaccharides induce apoptosis and inhibit CRC cell migration and invasion via the LPS/TLR4/NF-κB pathway, showing potential for CRC metastasis prevention. Modified citrus pectin blocks galectin-3, reducing CRC growth and liver metastasis by preventing cell aggregation. SBPW3, from Scutellaria barbata, inhibits TGF-β1-induced EMT and reduces liver metastasis in animal models[14-15]. Inositol hexaphosphate (IP6) and inositol suppress CRC liver metastasis, with combined use being more effective by regulating extracellular matrix proteins and the Wnt/β-catenin signaling pathway. These plant-derived polysaccharides show strong potential in CRC metastasis treatment.

9. Conclusion

Natural compounds, with their diverse structures, hold significant potential for treating colorectal cancer (CRC) metastasis. These plant-derived molecules offer multi-target benefits, blocking multiple signaling pathways, and can enhance the effectiveness of other therapies while reducing resistance. Despite centuries of use, the research and development of plant-based compounds is slow, with many plants still underexplored. The discovery of novel natural compounds for drug-resistant and metastatic CRC is crucial for advancing cancer treatment and warrants greater attention.

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