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Natural products modulating MAPK for CRC treatment: a promising strategy

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Colorectal cancer (CRC) is a common malignant tumor of the digestive system, and the pathogenic mechanism is still unclear, mostly related to genetics, immunity, inflammation, and abnormal activation of tumor-related signaling pathways. MAPK belongs to the Ser/Thr kinase family, which plays an important role in complex cellular programs such as the regulation of cell proliferation, differentiation, apoptosis, angiogenesis, and tumor metastasis. Increasing evidence supports that MAPK activation is highly correlated with the risk of CRC. Targeting MAPK may be a therapeutic strategy, and natural products show great therapeutic potential in regulating MAPK-related proteins. In this paper, we searched PubMed, Web of Science and CNKI databases with keywords "colorectal cancer, natural products, MAPK pathway, ERK, P38, JNK" for relevant studies in the last 14 years from 2010 to 2024. This work retrieved 47 studies, aiming to provide new therapeutic strategies for CRC patients and lay the foundation for new drug development.

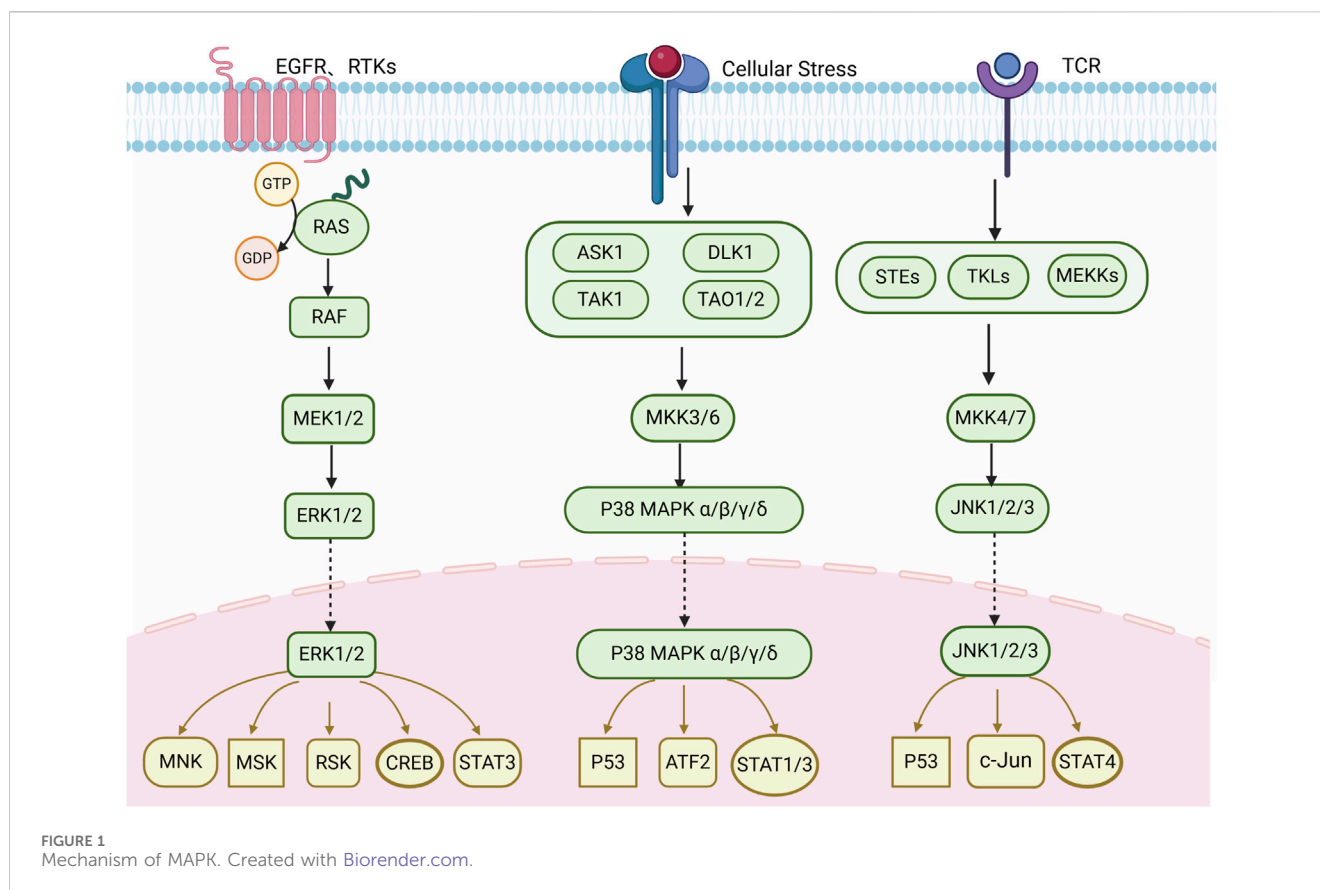
KEYWORDS

colorectal cancer, natural products, MAPK pathway, ERK, p38, JNK

1 Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer deaths globally in 2022, and the second and third most common cancers in women and men respectively (Siegel et al., 2024). Currently, clinical treatments for colorectal cancer include surgery, radiotherapy and chemotherapy, but all of them have poor prognosis and drug resistance, which seriously reduce the survival and quality of life of CRC patients. Therefore, seeking new therapeutic strategies has become an urgent problem nowadays. In recent years, botanical drugs have shown strong therapeutic potential in the treatment of oncological diseases. With the characteristics of multi-targets, low side effects and good efficacy, botanical drugs can inhibit tumor development by inhibiting the EMT process, blocking angiogenesis, regulating apoptosis and autophagy, promoting cell cycle arrest, and inhibiting the proliferation, invasion and migration of cancer cells, and it has been widely applied to a variety of oncological diseases, such as gastric cancer, hepatocellular carcinoma, and breast cancer (Wang K. et al., 2021). Mitogen-activated protein kinase (MAPK) is a serine/threonine-specific protein kinase, and activated MAPK is involved in the regulation of cell proliferation, differentiation, apoptosis, angiogenesis and tumor metastasis (Widmann et al., 1999).

Astragaloside IV (AS-IV), a triterpenoid extracted from botanical drug *Astragalus mongholicus* Bunge, has anti-inflammatory, anti-oxidative stress, and anti-tumor effects.



Jiang et al. (2017) found that AS-IV inhibited the activation of MAPK in MDA-MB-231 breast cancer cells, thereby inhibiting cell proliferation and invasion. In addition, Holothurin A (HA), a triterpenoid saponin extracted from *Holothuria scabra*, inhibited P38 MAPK and Akt/JNK and blocked the EMT process in PC3 cells of prostate cancer by upregulating the expression of E-cadherin and downregulating the expression of waviness proteins, twist1, slug and snail (Janta et al., 2023).

Aberrant activation of the MAPK pathway is closely associated with the development of many cancers, and studies suggest that natural products can intervene in MAPK, which is a potent therapeutic strategy for tumor treatment. Notably, the MAPK is also involved in chemotherapy resistance in CRC cells, and the sensitivity of CRC cells to drugs can be enhanced by modulating MAPK. In addition, inhibiting the activation of p38δ MAPK suppresses the growth of CRC cells, improves the efficacy of 5-FU, and overcomes drug resistance to some extent (Stramucci and Bossi, 2019).

Plenty of natural products are candidates for the treatment of CRC, and these metabolites have been shown to act by modulating MAPK-related protein molecules. Thus, these natural products could be complementary and alternative treatments for CRC.

2 Overview of the MAPK signaling pathway

The MAPK pathway is involved in the regulation of a variety of cellular physiological and pathological processes, including cell

proliferation, differentiation, and apoptosis. This signaling pathway also plays an important role in a variety of diseases, such as tumorigenesis, cardiovascular diseases, and immune cell activation (Lee et al., 2020). The MAPK family involved in mammals mainly includes extracellular regulating kinase (ERK), p38 mitogen-activated protein kinase (p38 MAPK/p38) and c-Jun N-terminal kinase (JNK) signaling pathways (Fang and Richardson, 2005) (Figure 1).

2.1 ERK1/2

The ERK (classical MAPK pathway) is crucial for cells to respond to external stimuli like growth factors. It activates cell cycle and anti-apoptotic proteins, driving cell-cycle progression and escaping programmed cell death (Martin-Vega and Cobb, 2023). Ras small GTPase (RAS) is activated by GTP/GDP exchange factors (GEFs) in response to stimuli such as receptor tyrosine kinases (RTKs) and EGFR (epidermal factor receptor). Activated RAS recruits RAF to the cell membrane and activates RAF. Then, activated RAF phosphorylates and activates MEK1/2 (Song et al., 2022a). MEK1/2 phosphorylate ERK1 (T202/Y204) and ERK2 (T183/Y185). Phosphorylated ERK translocates to the nucleus, activating transcription factors that regulate cell processes like proliferation, survival, growth, metabolism, migration, and differentiation (Ullah et al., 2022). KRAS and BRAF mutations are common in cancer cells. Aberrant ERK activation promotes tumor growth, survival, invasion, metastasis,

extracellular matrix degradation, and angiogenesis (Asl et al., 2021). Zhao et al. (2017) found that increased ERK expression can promote migration and invasion. Jenkins et al. (2023) showed that MAPK/ERK inhibitors can suppress proliferation and angiogenesis.

2.2 p38 MAPK

The p38MAPK cascade, also called the p38 pathway, is involved in cellular stress, immune response and inflammation. It has four isoforms: p38 α (MAPK14), p38 β (MAPK11), p38 γ (MAPK12) and p38 δ (MAPK13) (Han et al., 2020). A variety of stimuli such as oxidative stress, genotoxic and DNA damaging agents, inflammatory cytokines, PAMPs (Pathogen-Associated Molecular Patterns) and DAMPs (Danger-Associated Molecular Patterns) can activate p38 (Kyriakis and Avruch, 2012). Signals are transmitted via a complex network of signaling molecules, often activating small GTPases (Rac and CDC42), sometimes through activating interactions of adaptor proteins, and then activating protein kinases in the MAP4K or direct MAP3K layer of the p38 cascade (Sanz-Ezquerro and Cuenda, 2021). Activated p38 accumulates transiently and moves to the nucleus, activating downstream signaling proteins that regulate processes like RNA splicing, cytokine production, inflammatory responses, apoptosis, autophagy and cell cycle arrest (Wang et al., 2019). Kassassir et al. (2023) found that inhibiting p38 phosphorylation reduced the proliferation and invasion of CRC cells. Huang et al. (2023) reported that inhibiting IFI6 reversed OXA resistance in CRC cells by promoting ROS-induced p38. These studies suggest that regulating the p38 pathway may be a new approach for developing drugs to treat CRC in the future.

2.3 JNK

The JNK pathway (c-Jun N-terminal Kinases), also called the stress-activated protein kinase pathway, is crucial in cellular stress responses like regulating cell death and inflammatory responses (Wu et al., 2019). Encoded by JNK1, JNK2, and JNK3 genes, it's mainly activated by MKK4 and MKK7. When cells are stressed by irritants, growth factors or cytokines, the JNK pathway is activated. The activation signal passes through the Ras superfamily of G proteins to MLK, then activates MKK4/7 and downstream JNK (Tam and Law, 2021). The JNK pathway is important for apoptosis, inflammation, cytokine production and metabolism. Li et al. (2021a) showed that silencing JNK can inhibit CRC cell expansion. Alotaibi AG et al. (2021) also found that inhibiting JNK could reduce TNF- α -induced DNA damage and improve the RC tumor microenvironment.

3 Mechanism of MAPK in CRC

3.1 MAPK is involved in the regulation of cellular activity

MAPK pathway significantly regulates CRC cell growth, proliferation, migration, and invasion. Xu G. et al. (2023)

discovered that CEMIP, a cell migration-inducing protein, activated the CDC42/MAPK signaling pathway by enhancing the ubiquitination and degradation of the tumor suppressor GRAF1, promoting the shift from an epithelial to a mesenchymal phenotype, and ultimately facilitating the migration and invasion of HCT116 and SW480 cells. Li et al. (2021b) found that in CRC cells, the transcription factor RBP-J was highly expressed compared to normal tissues which elevated the expression of Tiam1, phosphorylates p38 MAPK, Slug-1, Twist1, and MMP-9, promoting the proliferation, migration, and invasion. Jin Y. et al. (2022) reported that increasing the level of p-JNK activated the MAPK downstream transcription factor ATF2, which then activated UCA1 to promote the migration and invasion of CRC cells. Collectively, these studies indicate that activated MAPK promotes CRC cell growth, proliferation, migration, and invasion through multiple mechanisms which include facilitating the epithelial-mesenchymal transition, decreasing the levels of proteins like Slug, waveform, increasing Slug-1, and Twist1, and inducing the activation of relevant transcription factors.

3.2 MAPK mediates autophagy and apoptosis in CRC

Cellular autophagy is an intracellular self-degradation and recycling process vital for maintaining intracellular homeostasis, removing damaged metabolites, responding to stress, and regulating cell growth and survival. It occurs in four stages: induction/activation, nucleation/extension, autophagosome-lysosome fusion, and content degradation. Studies indicated that autophagy play a significant role in cancer development (Debnath et al., 2023). P38 MAPK is an important autophagy-related protein, which activated via TAK1-MKK3/6-p38 and ASK1-MKK3/6-p38. Activated p38 phosphorylates Atg5 at T75, inhibiting autophagic membrane elongation and the LCII to LCIII conversion, thus suppressing the autophagy pathway (Keil et al., 2013). Regulating p38 expression can inhibit colorectal cancer cell growth and offer an effective CRC treatment method. Zheng et al. (2020) demonstrated that in HCT116 and HT29 cells, inhibiting PRDX2 reduced p38 phosphorylation, lowered the LC3II/I ratio, increased P62 expression, and decreased Beclin 1 expression, disrupting autophagy's protective effect and increasing apoptosis. Conversely, Stramucci et al. (2019) found that silencing MKK3 decreased p38 δ MAPK phosphorylation, reduced the late autophagosome marker p62/SQSTM1 levels, and increased the LC3II/LC3I ratio, inducing cellular autophagy and inhibiting tumor survival in HT29 and HCT-116 cells.

Apoptosis is a precisely regulated programmed cell death, occurring in development and aging, and maintaining cell populations in tissues. It has two main caspase-mediated pathways: the intrinsic pathway, releasing cytochrome c from mitochondria and controlled by bcl-2 family proteins (anti-apoptotic bcl-2 and pro-apoptotic bax and bak), and the extrinsic pathway activated by death receptors like Fas and other tumor necrosis factor receptor family members. The MAPK signaling pathway is crucial in apoptosis regulation. Eukaryotic elongation factor 1 A1 (eEF1A1) overexpression promotes CRC proliferation. Fan et al. (2023) found that silencing eEF1A1 in RKO and

Caco2 cells was able to downregulate ERK, p38, JNK phosphorylation, to reduce PCNA expression, to upregulate cleaved-caspase 3, Bax and to downregulate Bcl-2, inducing apoptosis and inhibiting cell proliferation. MicroRNA-125, a highly conserved miRNA, could target and downregulate VEGF, inhibit the downstream MAPK signaling pathway (decreasing ERK, p38, and JNK phosphorylation), enhance caspase-3 activity, increase DNA fragmentation, inducing apoptosis in RKO cells (Wu et al., 2018). The above studies show that during CRC formation, the balance between cell growth and apoptosis is disrupted. MAPK activation regulates multiple transcription factors, increasing pro-apoptotic protein expression and decreasing anti-apoptotic protein expression, thus inducing apoptosis in CRC cells.

3.3 MAPK and oxidative stress

Oxidative stress occurs when there's an imbalance between reactive oxygen species (ROS) and antioxidants. ROS play roles in cell processes like proliferation, differentiation, migration, apoptosis, and necrosis (Ebrahimi et al., 2020). Excessive formation of ROS leads to a disruption of redox homeostasis, which in turn leads to oxidative stress, often regulating the MAPK signaling pathway. Oxidative stress can activate JNK and p38 MAPK, inducing the co-stimulatory molecule CD80, activating the transcription factor STAT3, and influencing CRC development in terms of immune defense (Marchiori et al., 2019). MLK3, a MAP3K, has kinase-independent activation. Schroyer et al. (2018) found that oxidative stress activates ERK1/2, phosphorylates MLK3 at Ser705 and Ser758, promotes its interaction with B-Raf to activate ERK1/2, forming the ERK1/2-MLK3-B-Raf-MEK1/2-ERK1/2 mechanism, which promotes H₂O₂-treated HCT116 cell invasion. Jiang et al. (2023) discovered that in HCT116 cells, p20BAP31 was highly upregulated, which upregulated ROS levels and activated JNK phosphorylation, leading to mitochondria-dependent apoptosis and S-phase cell cycle arrest. Meng et al. (2018) cultured SW480 cells with quinuclidin (1,2,5,8-tetrahydroxyanthraquinone), and found it was able to produce ROS in a time-dependent manner, to increased JNK and p38 phosphorylation, to decreased ERK phosphorylation, inducing caspase-3-dependent apoptosis and causing G2/M-phase cell cycle arrest by activating p53, upregulating Bad, downregulating Bcl-2. ROS scavenger NAC inhibits these processes. Overall, oxidative stress-induced ROS affect cell processes and CRC-related events through MAPK and other molecular mechanisms.

3.4 MAPK and pathologic angiogenesis

Angiogenesis is the formation of new blood vessels from existing capillaries, regulated by pro- and anti-angiogenic factors (Lugano et al., 2020). Malignant tumors rely on angiogenesis due to enormous demand for nutrients, oxygen and natural aggressiveness. The MAPK pathway is involved in angiogenesis regulation. ELK4, a MAPK downstream target, regulates the transcription factors SP1 and SP3, activates the transcription of pathological neoangiogenic factor LRG1, and promotes tumor angiogenesis, cell proliferation, and migration in HCT116 and

LoVo cells (Zhu et al., 2023a). Klemke et al. (2021) found that macrophage migration inhibitory factor (MIF) promotes angiogenesis and cell proliferation in HCT116 cells by activating the CD74 receptor, increasing phosphorylation of p38 and ERK, and upregulating the expression of VEGF and IL8. In an AOM/DSS-constructed CRC mouse model, the p38MAPK pathway was activated and its key effector kinase MK2 increased the expression of pro-angiogenic factors Serpin-E1 and Cxc-12, promoting tumor angiogenesis and metastasis (Suarez-Lopez et al., 2021). Elevated MicroRNA 452 in Caco2 cells, could significantly decrease VEGFA protein levels and inhibit the KRAS-BRAF-MAPK pathway. *In vitro* experiment also demonstrated that MicroRNA 452 could decrease the expression of angiogenic marker CD31 and inhibit angiogenesis (Mo et al., 2019). Upregulated ILT4 (Immunoglobulin-like transcript 4) in SW620 and HCT116 cells was able to activate the ERK pathway and upregulate the levels of VEGF-A and FGF-1, promoting angiogenesis, while downregulating ILT4 enhances bevacizumab's anti-vascular and anti-tumor ability (Liu J. et al., 2023). In summary, multiple factors and molecules, including those related to the MAPK pathway, either promote or inhibit angiogenesis in CRC cells and mouse models through different mechanisms.

4 Natural products inhibit CRC by regulating MAPK

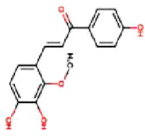
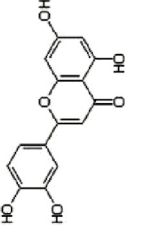
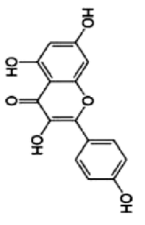
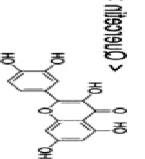
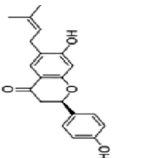
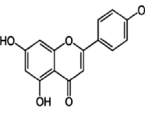
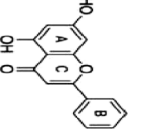
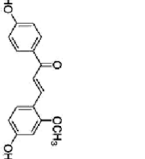
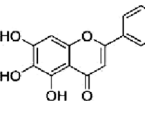
Numerous experimental findings have demonstrated that natural products can exert beneficial effects on colorectal cancer (CRC) treatment. By modulating the MAPK signaling pathway, they can enhance the state of pathological tissues, suppress the proliferation and migration capabilities of tumor cells, and reduce drug resistance. These properties indicate natural products with a significant role in CRC treatment, thus providing a reliable theoretical foundation for the utilization of natural products in treating CRC. In this review, a total of 60 articles were retrieved. After excluding 13 articles, 47 remained. The majority of these were cellular experiments, with 10 involving animal experiments. The review covered 10 types of flavonoids, 11 types of terpenes, 7 types of saponins, 2 types of polyphenols, 5 types of alkaloids, and 12 types of other metabolites, as shown in Table 1.

4.1 Flavonoids

Flavonoids are important bioactive metabolites that are widely found in a variety of plant medicines. Existing studies on flavonoids mainly focus on antioxidant, anticancer effects (Slika et al., 2022). Some flavonoids, such as licorice chalcone, lignans, kaempferol, and quercetin, have good anti-CRC effects.

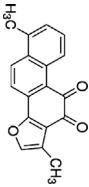
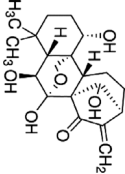

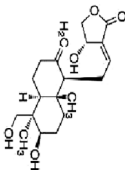
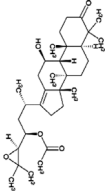
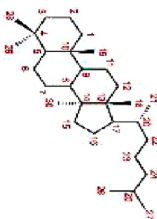
Licochalcone B (LCB), a flavonoid extracted from the botanical drugs such as *Glycyrrhiza glabra* L, can treat NLRP3 inflammatory vesicle-associated disorders (Li Q. et al., 2022). Kwak et al. (2023a) cultured oxaliplatin-resistant (OxR) colorectal cancer cells (HCT116-OxR) with different concentrations (10, 20, and 30 μM for 24, 48 h) of LCB. The results showed that LCB significantly upregulated the phosphorylation of JNK and p38 MAPK through ROS-mediated pathways in a dose-dependent manner, and

TABLE 1 Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|----------------|---------------------------------------|---|---|--|--|----------------------------|
| Licochalcone B | <i>Glycyrrhiza glabra</i> L. |  | HCT116-OxR cells | JNK↑ p38 MAPK↑ p21↑ p27↑ B1↓ cdc2↓ | G2/M cell cycle arrest Inhibit proliferation Induce apoptosis | Kwak et al. (2023a) |
| Luteolin | <i>Lonicera japonica</i> Thunb |  | HCT-116 cells HT-29 cells BALB /c nude mice | p-MEK1↓ p-ERK1/2↓ BCL-2↓ BAX↑ cleaved caspase-3↑ | DNA damage Induce apoptosis G2 cell cycle arrest Reduce tumor weight and volume | Song et al. (2022a) |
| | | | HT-29 cells | JNK↑ p38↑ ROS↓ SOD↑ CAT↑ | Induces apoptosis | Kang et al. (2017) |
| Kaempferol | <i>Kaempferia galanga</i> L. |  | HCT116 cells HCT15 cells | ROS↑ p38 MAPK↑ caspase-8↑ -9↑ -3↑ cleaved PARP↑ | Induce apoptosis | Choi et al. (2018) |
| | | | 5-FU-resistant LS174-R cells | P38↑ P21↑ p53↑ Ser15↑ p-cdc2↓ p27↓ | Induce apoptosis Inhibit tumor growth | Riahi-Chebbi et al. (2019) |
| Quercetin | <i>Agrimonia pilosa</i> Ledeb |  | RKO cells SW480 cells HCT116 cells Balb/c nude mice | JNK↑ E-calmodulin↑ waveform protein↓ N-calmodulin↓ | Inhibit invasion Inhibit migration Inhibit Tumor growth | Trinh et al. (2022) |
| Bavachin | <i>Cullen corylifolium</i> Medik |  | HT29 cell HCT 116 cells Balb/c nude mice | p38↑ ERK↑ JNK↑ Gadd45a↑ PARP↑ cleaved Caspase-3↑ | Induce apoptosis Inhibit Tumor growth | Wang et al. (2023) |
| Apigenin | <i>Apium graveolens</i> L. |  | SW480 cells HCT-116 cells | P38 MAPK ↓ Bax↑ cleaved caspase-3↑ Bcl-2↓ MMP2↓ MMP9↓ Snail↓ E-calmodulin↑ | Induce apoptosis Inhibit cell growth and metastasis | Zhang et al. (2021) |
| Chrysin | <i>Oroxylum indicum</i> L. |  | | | | |
| Echinatin | <i>Trigonella foenum-graecum</i> L. |  | HT116 cells HT29 cells HCT116-OxR cells HT29-OxR cells | ROS↑ GRP78↑ CHOP↑ p-JNK↑ p-p38↑ | G2/M cell cycle arrest Induce apoptosis | Kwak et al. (2023b) |
| Baicalein | <i>Scutellaria baicalensis</i> Georgi |  | HCT 116 cells | JNK↑ ERK↑ p38↑ DEPP↑ Gadd45a↑ Cleaved caspase-3↑ -9↑ | Induce apoptosis | Su et al. (2018) |

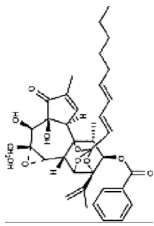
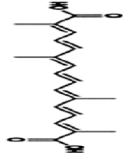
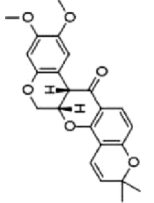
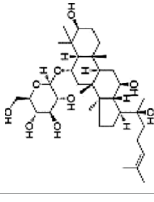
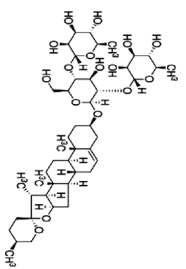
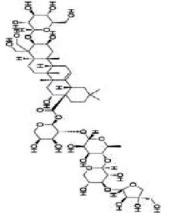
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TABLE 1 (Continued) Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|--------------------------------|---|---|----------------------------|--|---|---------------------------|
| Origanum majoana Essential Oil | <i>Origanum vulgare</i> L. | ----- | HT-29 cells | P38 MAPK↑ Cleaved p70S6K↑ caspase-3↑ TNF-α↑ | Induce apoptosis | Athamneh et al. (2020) |
| Tanshinone I | <i>Salvia miltiorrhiza</i> Bunge |  | HCT116 cells HT29 cells | Cleaved PARP↑ tBid↑ caspase-3↑ -8↑ p38↑ JNK↑ | Induce apoptosis | Kim et al. (2018) |
| Oridonin | <i>Isodon rubescens</i> (Hemsl.) |  | HCT116 cells | p-p38↑ BMP7↑ Bad↑ Bcl-2↓ | G2 cell cycle arrest Inhibit proliferation Induce apoptosis | Ren et al. (2016) |
| Cryptotanshinone | <i>Salvia miltiorrhiza</i> Bunge |  | SW620-Ad300 cells | LC3-II↑ ROS↑ P38 MAPK↑ NF-kB↑ | Induce autophagy | Xu et al. (2017) |
| Andrographolide | <i>Andrographis paniculata</i> (Burm.f.) Wall. ex Nees |  | HCT116 cells | NADPH↓ ERK1/2↓ P38 MAPK↓ IL-8↓ | Inhibit angiogenesis | Yuan et al. (2018) |
| Alisol B 23-acetate | <i>Alisma plantago-aquatica</i> subsp. orientale (Sam.) Sam |  | C57BL/6J mice | p38-MAPK↓ERK↓ JNK↓ IL-6↓ TNF-α↓ IFN-γ↓ IL-10↑ | Prevention of CAC | Zhu et al. (2021) |
| TS essential oil | <i>Thymus algeriensis</i> Boiss. & Reut | ----- | HCT116 cells | ERK1/2↑ JNK↑ p38↑ DR5↑ SP1↑ CHOP↑ | Induce apoptosis | Guesmi et al. (2021) |
| Ganoderma lucidum triterpenes | <i>Ganoderma lucidum</i> (Curtis) P. Karst |  | HT-29 cells | p-p38↓ Beclin-1↑ LC-3↑ | Induce autophagy | Thyagarajan et al. (2010) |

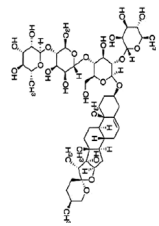
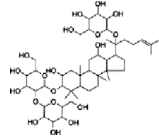
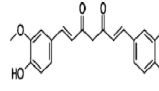
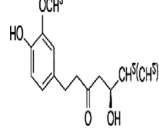
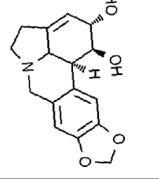
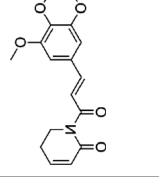
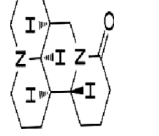
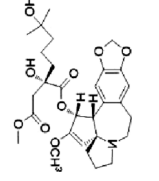
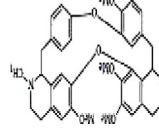
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TABLE 1 (Continued) Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|-------------------------|---|---|---------------------------------|--|---|----------------------|
| Yuanhuacine | <i>Daphne genkwa Siebold & Zucc</i> |  | HCT116 cells | p38 MAPK↑ p21 mRNA↑ | Induced cell arrest in G2/M phase | Zhang et al. (2014) |
| Crocin | <i>Crocus sativus L</i> |  | HCT-116 cells | p-p38 MAPK↑ VEGF↓ MMP-9 mRNA↓ | Inhibit proliferation Inhibit invasion Inhibit angiogenesis | Khajeh et al. (2020) |
| Deguelin | <i>Mundulea sericea (Willd.) A.Chev</i> |  | SW620 cells RKO cells | p38 MAPK↑ cleaved caspase-3↑ cleaved PARP↑ Bcl-2↓ | Inhibit proliferation Induce apoptosis | Chen et al. (2018) |
| Ginsenoside Rh1 | <i>Panax ginseng C. A. Mey.</i> |  | SW620 cells BALB/c nude mice | p-P38/P38↓ p-ERK1/2/ERK1-2 ↓ p-JNK/JNK↓ MMP1↓ MMP3↓ TIMP3↑ | Inhibit invasion and migration Inhibit Tumor growth | Lyu et al. (2019) |
| Rhizoma Panacis Majoris | <i>Panax bipinnatifidus var. bipinnatifidus</i> | ----- | HCT116 cells SW620 cells | p-JNK/JNK↑ p-p38/p38↑ p-ERK/ERK↓ Bcl-2↓ Bcl-xL↓ Mcl-1↓ | Induced apoptosis Blocked cell cycle in G0/G1 and S phase | Chang et al. (2021) |
| Dioscin | <i>Dioscorea panthaica Prain & Burkill</i> |  | RKO cells HT-29 cells | JNK↑ p38 MAPK↑ caspase-3↑ -9↑ cleaved PARP↑ | Induce apoptosis | Li et al. (2014) |
| | | | C26 derived tumor mouse | VEGF↓ p-ERK1/2↓ | Inhibit angiogenesis | Tong et al. (2014) |
| Platycodin D | <i>Platycodon grandiflorus (Jacq.) A.DC</i> |  | HT-29 cells | p-p38↑ Bax↑ Cleaved PARP↑ Bcl-2↓ | Induce apoptosis | Han et al. (2024) |

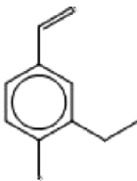
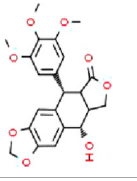
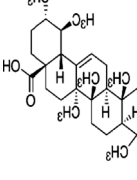
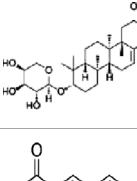
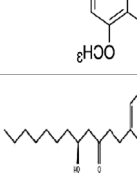
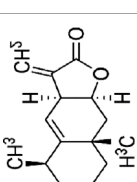
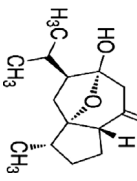
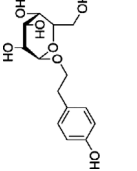

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TABLE 1 (Continued) Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|----------------------------------|--|---|--|---|--|-----------------------------|
| Paris saponin VII | <i>Trillium tschonoskii</i> Maxim |  | HT-29 cells SW-620 cells | D1↓ Cdk-4↓ Cdk-6↓ ERK1/2↓ Cleaved caspase-3↑ -9↑ PARP↑ Bax↑ Bcl-2↓ | G1 cell cycle arrest Induce apoptosis | Li et al. (2014) |
| Gynostemma pentaphyllum saponins | <i>Gynostemma pentaphyllum</i> (Thunb.) Makino |  | ApcMin/+ CRC mice | Prdx1↑Prdx2↑ Raf-1↓ RAS↓ RAF↓ MEK↓ ERK↓ | Reduce the number and size of intestinal polyps | Tai et al. (2016) |
| Curcumin | <i>Curcuma longa</i> L |  | CT26 cells | P38 MAPK↓ HPSE↓ | Inhibit invasion Inhibit migration | Li et al. (2020) |
| [6]-Gingerol | <i>Zingiber officinale</i> Roscoe |  | SW-480 cells | ERK1/2↓ JNK↓ Caspase -3↑ -7↑ Cleaved PARP↑ | Induce apoptosis | Radhakrishnan et al. (2014) |
| Lycorine | <i>Lycoris radiata</i> (L'Hér.) Herb |  | CT-26 cells HCT116 cells HT-29 cells | E-calmodulin↑ N-calmodulin↓ β-linker↓ waveform protein↓ Snail protein↓ MAPK↓ | Block EMT | Gao et al. (2021) |
| Piperlongumine | <i>Piper longum</i> L |  | HT-29 cells | ROS↑ ERK↑ caspase-3↑ | Induce apoptosis | Randhawa et al. (2013) |
| Matrine | <i>Sophora flavescens</i> Aiton |  | CT26 cells | JNK↓ ERK↓ Cldn9↓ N-calmodulin↓ MMP2↓ MMP9↓ | Inhibit proliferation Inhibit invasion Inhibit migration | Du et al. (2023) |
| Homoharringtonine | <i>Cephalotaxus hainanensis</i> H.L.Li |  | LoVo cells | EphB4↓ ERK1/2↓ Bcl-2↓ Mcl-1↓ | Induce apoptosis | Shi et al. (2020) |
| Tetrandrine | <i>Stephania tetrandra</i> S.Moore |  | CT-26 cells | P38 MAPK↑ | Induce apoptosis | Wu et al. (2010) |


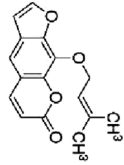
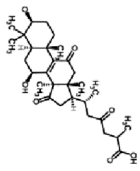
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TABLE 1 (Continued) Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|-----------------|---|---|---|--|--|-----------------------|
| Vanillin | <i>Vanilla pompona</i> Schiede |  | HT-29 cells SW480 cells Male BALB/c nude mice | ASK1-p38 MAPK↑ NNMT↓ | Induce apoptosis Inhibit tumor growth | |
| Podophyllotoxin | <i>Podophyllum versipelle</i> Hance |  | HCT116 cells | ROS↑ RP78↑ CHOP↑ p38 MAPK↑ | Oxidative Stress Induce apoptosis G2/M cell cycle arrest | Lee et al. (2021) |
| Ursolic acid | <i>Prunella vulgaris</i> L. |  | SW620/RKO cells | p-MEK1/2↓ p-ERK1/2↓ p-p38↓ p-JNK↓ caspase-3↑ -9↑ -8↑ Bcl-xL↓ Bcl-2↓ Ki-67↓ | Induce apoptosis | Shan et al. (2016) |
| Di Yu | <i>Sanguisorba officinalis</i> L. |  | RKO-R cells HCT15-R cells. | Ras/MEK/ERK↓ Bax↑ cleaved caspase-3↑ -9↑ cleaved PARP↑ | Enhancing the chemosensitivity to 5-FU Inhibit migration | Zhang et al. (2023) |
| Ferulic acid | <i>Angelica sinensis</i> (Oliv.) Diels |  | CT26 cells Balb/c mice | JNK↑ ERK↑ BAX↑ LC3-II↑ BCL-2↓ | Induce apoptosis Induce autophagy | Chen et al. (2023) |
| 8-Gingerol | <i>Zingiber officinale</i> Roscoe |  | HCT116 cells DLD1 cells | EGFR/STAT/ ERK↓ D1↓ c-Myc↓ MMP2↓ | Induced cell cycle arrest in the G0/G1 phase Inhibit proliferation Inhibit migration | Hu et al. (2020) |
| Alantolactone | <i>Inula helenium</i> L. |  | HCT116 cells RKO cells | ROS↑ JNK↑ P38MAPK↑ | Inhibit proliferation Induce apoptosis | Cao et al. (2019) |
| Curcumol | <i>Curcuma longa</i> L. |  | LoVo cells BALB/c athymic nude | IGF-1R↓ p38↑ Bax/Bcl-2↑ | Induce apoptosis Inhibit tumor growth | Wang et al. (2015) |
| Salidroside | <i>Rhodiola rosea</i> L. |  | HT29 cells | HT29↑ p-JNK↑ p38 MAPK↑ caspase -3↑ -8↑ | Induce apoptosis | El-Kott et al. (2021) |

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TABLE 1 (Continued) Natural products against colorectal cancer by modulating MAPK.

| Extract | Origination | Structure | Model | Biological effects | Results | References |
|----------------------------------|---|---|-----------------------------|---|---|--------------------|
| Sulforaphane | <i>Brassica oleracea</i> L. |  | HT-29 cells | ROS↓ MAPK↓ IL-1β↓ IL-6↓ | Inhibit proliferation Inhibit migration | Sah et al. (2024) |
| Imperatorin | <i>Angelica dahurica</i> (Hoffm.) Benth. & Hook.f. ex Franch. & Sav |  | HCT116 cells | ERK1/2↓ JNK↓ p38 MAPK↓ HIF-1α↓ VEGF↓ CD31↓ | Inhibit proliferation Inhibit angiogenesis | Mi et al. (2017) |
| Ganoderma lucidum polysaccharide | <i>Ganoderma lucidum</i> (Curtis) P. Karst |  | HT-29 cells HCT116 cells | p-ERK↑ LC3-II↓ p62↓ | Induce apoptosis | Pan. et al. (2019) |

decreased the protein levels of cyclin B1 and cdc2 meanwhile increased the protein levels of p21 and p27, ultimately inducing cell cycle arrest in G2/M phase, apoptosis, which could be reversed by the JNK and p38 Inhibitor SP600125 and SB203580.

Luteolin is a flavonoid extracted from many botanical drugs such as *Lonicera japonica* Thunb, is used in the treatment of colon, lung, and prostate cancers (Çetinkaya and Baran, 2023). Song et al. (2022b) reported that Luteolin (0, 10, 20, and 40 μM) was able to dose-dependently reduce the levels of p-MEK1 and p-ERK1/2, to decrease the expression of BCL-2, to elevated the expression of BAX, cleaved caspase-3, inducing apoptosis and DNA damage, and arresting the cell cycle in G2 phase in HCT-116 and HT-29 cells. *In vivo*, high-dose (40 mg/kg/d) luteolin effectively inhibited tumor growth. Kang et al. (2017) showed that luteolin (5, 10, 25, 50, 200 μg/mL) could dose-dependently increase the phosphorylation of JNK and p38 MAPK, and induce apoptosis through antioxidant effects.

Kaempferol, a major metabolite of the botanical drug *Kaempferia galanga* L, which has antioxidant, anti-inflammatory, and cardioprotective activities (Chen et al., 2024). Riahi-Chebbi et al. (2019) found that 75 μM kaempferol in combination with 60 μM 5-FU was able to induce apoptosis by inhibiting the p38 MAPK pathway and downregulating the expression of phosphorylated-cdc2 and p27 in 5-FU-resistant LS174-R cells. Meanwhile, the combination can reduce the level of VEGF-A and IL-8 and inhibit tumor growth. Choi et al. (2018) reported that kaempferol (0, 12.5, 25, 50 and 100 μM for 24, 48, and 72 h) upregulated the expression of p-p38 MAPK, downregulated the expression of p-JNK and p-ERK, inducing apoptosis in HCT116 and HCT15 cells in a dose- and time manner. The above effects were reversed with the addition of p38 MAPK inhibitor SB203580.

Quercetin is a flavonoid widely found in *Agrimonia pilosa* Ledeb which can treat a variety of cancers such as breast, colorectal, and liver cancer (Maugeri et al., 2023). Trinh et al. (2022) demonstrated that Quercetin (0, 2, 5, 20 and 50 μM for 24,48,72 h) inhibited the invasion,metastasis and effectively induced the MET process in

SW480, HCT116 cells by activating JNK, upregulating the expression of E-calmodulin, and downregulating the expression of waveform protein, N-calmodulin. This process can be reversed by JNK inhibitor SP600125. Quercetin could also effectively inhibited the growth of solid tumors in Balb/c nude mice.

Apigenin and chrysin are flavonol flavonoids derived from *Apium graveolens* L and *Oroxylum indicum* L, which have anti-inflammatory and antioxidant properties (Lee et al., 2023; Farkhondeh et al., 2019). Zhang et al. (2021) reported that the combination of apigenin (25 μM) and chrysin (25 μM) inhibited the activity of P38-MAPK/AKT and had a synergistic inhibitory effect on the growth and metastasis of SW480 and HCT-116 cells as compared to the treatment alone. P38 agonist anisomycin can adverse the above process.

Bavachin, a dihydroflavonoid isolated from botanical drugs such as *Cullen corylifolium* Medik, has been used in the treatment of neurological disorders (Wang Y. et al., 2021). Wang et al. (2023) found that Bavachin (20, 30, and 40 μmol·L⁻¹ for 24h, 48 h) increased the phosphorylation level of p38/ERK/JNK in a dose-dependent manner, and upregulated the expression of Gadd45a, cleaved PARP and cleaved Caspase-3, inducing apoptosis and inhibiting tumor growth in HT29 and HCT 116 cells.

Echinatin (Ech), a natural flavonoid extracted from the botanical drug *Trigonella foenum-graecum* L, which has anti-inflammatory properties (Xu et al., 2021). Kwak et al. (2023b) found that Ech (5, 10, and 15 μM) was able to dose-dependently increase ROS levels, to upregulate the expression of GRP78, CHOP, to increase p-JNK and p-p38, inducing apoptosis caused by caspase activation, and blocking the cell cycle at G2/M in oxaliplatin-resistant (HCT116-OxR and HT29-OxR) cells. The inhibitory effects could be abrogated by the JNK inhibitor SP600125 and the p38 inhibitor SB203580.

Baicalein, a flavonoid with anti-inflammatory and anti-tumor effects extracted from the botanical drugs such as *Scutellaria baicalensis* Georgi (Tuli et al., 2020). Su et al. (2018) reported that Baicalein (10, 20, 400 μM for 6, 12, 24 h) was able to dose-

dependently upregulate the levels of DEPP, Gadd45a which induced growth arrest and DNA damage, to activate MAPK (JNK/ERK/p38 phosphorylation) which induced apoptosis in HCT116 cells.

The above findings suggest that flavonoids can mediate the MAPK signaling pathway to cause cell cycle arrest, inhibit cell proliferation and induce apoptosis.

4.2 Terpenes

Terpenes are a large group of organic metabolites found primarily in leaves, fruits, flowers, rhizomes, and plant roots. Terpenes can be categorized into five main groups: monoterpenes, sesquiterpenes, diterpenes, triterpenes, and heteroterpenes, which have anti-inflammatory, antioxidant, antibacterial, and antitumor properties (Silva-Reis et al., 2023). It has shown significant results in the treatment of CRC.

Origanum majorana Essential Oil (OME), a terpenoid metabolite extracted from the botanical drug *Origanum vulgare* L, could be used to treat acne (Taleb et al., 2018). Athamneh et al. (2020) reported that OME (256 µg/mL) promoted endogenous and exogenous apoptosis in HT-29 cells by activating p38 MAPK, increasing cleaved p70S6K, and upregulating expression of TNF-α.

Tanshinone I (Tan I), a natural diterpenoid quinone metabolite extracted from botanical drugs such as *Salvia miltiorrhiza* Bunge, has been used to treat with osteosarcoma (Ye et al., 2022). Study (Kim et al., 2018) have shown that Tan I (0, 15, 30, 60, 90, 120 µM for 24 h) dose-dependently activated cleaved PARP, tBid, caspase-8, -3, and upregulated the phosphorylation of p38 and JNK, ultimately inducing apoptosis in HCT116 and HT29 cells. In addition, this experiment demonstrated that the phosphorylation of p38 MAPK was mediated by ROS.

Oridonin (ORI) is a diterpenoid extracted from *Isodon rubescens* (Hemsl.) H.Hara with strong anti-inflammatory and anti-cancer activities (Li X. et al., 2021). Ren et al. (2016) reported that ORI (0, 5, 10, 15, 20, 25 µM for 24, 48, 72 h) was able to dose- and time-dependently upregulate the levels of BMP7, Bad, and decrease the levels of Bcl-2, promoting apoptosis and arresting the HCT116 cells in the G2 period. Additional study revealed that BMP7 may mediate the antiproliferative effects of ORI in part through activation of p38 MAPK.

Cryptotanshinone (CTS) is also an active quinone diterpene isolated from many botanical drugs such as *Salvia miltiorrhiza* Bunge with anticancer, anti-inflammatory, and immunomodulatory pharmacological effects (Li H. et al., 2021). Xu et al. (2017) observed that CTS (10 µM) induced cell death by autophagy through the ROS-p38 MAPK-NF-κB signaling pathway in SW620-Ad300 cells, which could be blocked by the ROS inhibitor NAC or p38 inhibitor SB202190.

Andrographolide, the most abundant diterpene lactone in botanical drug *Andrographis paniculata* (Burm.f.) Wall. ex Nees, has been shown to alleviate cardiac dysfunction and reduce cardiac hypertrophy and fibrosis (Tian et al., 2023). Yuan et al. (2018) reported that Andrographolide (5,10,20,50 and 100 µM) dose-dependently inhibited NADPH oxidase activation, downregulated ERK1/2, P38 MAPK activation, and effectively suppressed angiogenesis in HCT116 Cells.

Alisol B 23-acetate (AB23A), a tetracyclic triterpenoid derived from botanical drug *Alisma plantago-aquatica subsp. orientale* (Sam.) Sam, which improves allergic asthma (Nam and Im, 2023). Zhu et al. (2021) observed that AB23A (50 mg/kg/day) significantly reduced the phosphorylation of p38-MAPK, ERK, JNK, and upregulated the expression of IL-10 in AOM/DSS colitis-associated cancer (CAC) mouse model, and interfered with the development of CAC.

The essential oil extract from the aromatic medicinal plants *Thymus algeriensis* Boiss. and Reut contains high levels of terpenoids, which can protect nerves (Rezq et al., 2020). Guesmi et al. (2021) reported TS essential oil (0.5–50 pg/mL) dose-dependently activated the ERK1/2, JNK, p38 MAPK, and upregulated the expression of DR5, SP1, CHOP, promoting HCT116 cells apoptosis.

Ganoderma lucidum triterpenes (GLT), a terpene metabolite with antiviral properties extracted from the botanical drug *Ganoderma lucidum* (Curtis) P. Karst (Ahmad et al., 2021). Thyagarajan et al. (2010) reported that GLT (0–1.0 mg/mL; 0–6 h) dose- and time-dependently inhibited phosphorylation of p38, and upregulated the expression of Beclin-1 and LC-3, inducing autophagy in HT-29 cells. P38 inhibitor SB202190 enhanced the processes.

yuanhuacine (YHL-14), a diterpenoid extracted from botanical drug *Daphne genkwa* Siebold & Zucc, can be used to treat lung and breast cancer (Bailey C. 2022). It was found that YHL-14 (2–16 µM) activated p38 MAPK, and upregulated p21 mRNA expression, inducing cell arrest in G2/M phase in HCT116 cells in a dose-dependent manner. (Zhang et al., 2014).

Crocetin, a water-soluble carotenoid which has neuroprotective properties and extracted from botanical drugs such as *Crocus sativus* L (Liu Z. et al., 2023). Khajeh et al. (2020) reported that Crocetin (400, 600, and 800 µM) dose-dependently increased the p-p38 MAPK, downregulated the expression of VEGF and MMP-9 mRNA in HCT-116 cells, thereby inhibiting cell proliferation, migration and angiogenesis. When the concentration of crocetin is 400, 600, 800 µM, the ratio of p-p38/p38 is 1.9, 2.2, 2.5 respectively.

Deguelin, a natural carotenoid extracted from *Mundulea sericea* (Willd.) A.Chev. was used to treat lung cancer (Gao et al., 2020). Chen et al. (2018) observed that Deguelin (0–200 µM for 24, 48 h) dose- and time-dependently induced apoptosis in SW620 and RKO cells by activating the p38 MAPK, upregulating cleaved caspase-3, cleaved PARP, downregulating Bcl-2, survivin. P38 MAPK inhibitor SB203580 can block proliferation inhibition. Vivo experiments also showed that Deguelin has an inhibitory effect on CRC.

The above findings suggest that terpenoids play an anti-proliferative, anti-CRC role by mediating MAPK activation of oxidative stress, causing cell cycle arrest, inhibiting angiogenesis, and inducing apoptosis and autophagy.

4.3 Saponins

Saponins are plant secondary metabolites with great structural and functional diversity, and are categorized into triterpene saponins and steroidal saponins according to the structure of the glycosides. Natural saponins in herbal medicine have anti-

inflammatory, antitumor, antioxidant, and antiviral effects (Zheng Z. et al., 2022). Therefore, the potential of saponins to inhibit CRC is worth investigating.

Ginsenoside Rh1 (Rh1), a tetracyclic triterpenoid saponin extracted from the botanical drug *Panax ginseng* C.A.Mey, is used to treat asthma and allergic inflammation (Jin et al., 2023). Lyu et al. (2019) reported that Rh1 (0, 50, 100 μ M) was able to suppress the migration and invasion of SW620 cells by decreasing the ratios of p-P38/P38, p-ERK1/2/ERK1-2 and p-JNK/JNK, downregulating the mRNA expression of MMP1 and MMP3, and upregulating the mRNA expression of TIMP3. The ratios of p-38/p38, p-JNK/JNK, p-ERK/ERK were 0.3, 0.2, and 0.6 respectively. *In vitro* experiments demonstrated that oral administration of Rh1 (20 mg/kg) significantly reduced CRC tumor weight.

Rhizoma *Panacis Majoris* (RPMTG), is a total saponin extracted from *Panax bipinnatifidus* var. *bipinnatifidus* that can be used in the treatment of rheumatoid arthritis (Ren et al., 2023). Chang et al. (2021) found that RPMTG (0, 100, 200, 250 μ g/mL) was able to dose-dependently increase the rate of p-JNK/JNK, p-p38/p38 and decrease p-ERK/ERK, inducing apoptosis and blocking cell cycle in G0/G1 and S phase in HCT116 and SW620 cells, respectively. The above effects were reversed with the addition of JNK inhibitor SP600125 and p38 inhibitor SB203580. In HCT116 cells, at RPMTG 100 and 250 μ g/mL, the relative protein levels of p-p38/p38 are about 1.4 and 2.5; in SW620 cells, about 1.1 and 2.

Dioscin, a naturally occurring steroidal saponin found in botanical drugs such as *Dioscorea panthaica* Prain & Burkill, has been shown to reduce oxidative stress and inflammation to minimize intestinal toxicity of chemotherapeutic drugs (Jin S. et al., 2022). Li et al. (2018) reported that Dioscin (0, 1.25, 2.5 and 5 μ g/mL for 0, 6, 12 h) time- and dose-dependently inhibited proliferation and promoted apoptosis in RKO, HT-29 cells, which may be related to the activation of JNK/p38 MAPK mediated by ROS. *Vivo* experiments confirmed that (Tong et al., 2014) Dioscin (30, 60 mg/kg) decreased blood vessel density and inhibited tumor growth in C26 mouse tumor model. Additional study showed that Dioscin downregulated the expression of VEGF, VEGFR2, FAK, Src, and p-ERK1/2, suggesting that Dioscin inhibits angiogenesis by regulating VEGF and MAPK.

Platycodin D (PD) is a triterpenoid saponin extracted from the botanical drug *Platycodon grandiflorus* (Jacq.) A.DC, which has antioxidant and cardiomyocyte protective effects (Wang et al., 2018). Han et al. (2024) found that PD (0, 10, 20 μ M) significantly increased the level of p-p38 and upregulated the expression of Bax, cleaved PARP, inducing apoptosis in HT-29 cells in a dose-dependent manner. When the concentrations of Platycodin D were 0, 10, and 20 μ M, the ratios of p-ERK/ERK, p-p38/p38, and p-JNK/JNK were approximately 1, 0.6, 0.2; 1, 2, 3.5; and 1, 3, 4.5, respectively.

Paris saponin VII, a steroidal saponin from the botanical drug *Trillium tschonoskii* Maxim, which can reverse chemotherapy resistance in breast cancer (Li et al., 2019). Li et al. (2014) reported that Paris saponin VII (0.5, 1.0, 1.5, 2, 2.5, 5 μ M for 24, 48 h) was effective in the treatment of HT-29 and SW-620 cells by inhibiting the Ras/MEK1/2/ERK1/2 pathway, increasing cleaved caspase-3-9, PARP, Bax, downregulating Bcl-2, and blocking the cell cycle in G1 phase.

Gynostemma pentaphyllum saponins (GpS), a triterpenoid saponin derived from the botanical drug *Gynostemma pentaphyllum* (Thunb.) Makino, can be used to regulate triglyceride and cholesterol (Xie et al., 2024). Study showed that GpS (500, 750 mg/kg) was able to dose-dependently upregulated the expression of Prdx1 and Prdx2, and downregulate the expression of Raf-1, which acted as an anticancer agent by inhibiting the RAS/RAF/MEK/ERK signaling pathway in ApcMin/+ CRC mice (Tai et al., 2016).

The above findings indicate that saponins are potential natural products to inhibit tumor development *in vitro* and *in vivo* by affecting MAPK, inhibiting angiogenesis, enhancing the efficacy of chemotherapeutic agents, and inducing apoptosis.

4.4 Polyphenols

Polyphenols are secondary metabolites, mainly of plant origin, and current research on polyphenols has focused on antioxidant, anti-inflammatory, and anti-tumor properties with a wide range of therapeutic benefits (Bruno and Ghiadoni, 2018; Roszkowski, 2023). Metabolites such as resveratrol, astragalus, and curcumin have been shown to modulate MAPK-induced CRC cell cycle arrest, DNA damage, and apoptosis, and inhibit proliferation and migration.

Curcumin, a natural polyphenol extracted from the botanical drug *Curcuma longa* L, which has anti-inflammatory, anti-cancer effects (Sadeghi et al., 2023). Li et al. (2020) reported that Curcumin (0.10 μ M) was able to downregulate the phosphorylation levels of STAT5 and P38, and decrease the expression of HPSE, effectively inhibiting migration and invasion in CT26 cells.

[6]-Gingerol, a polyphenolic metabolite extracted from the botanical drug *Zingiber officinale* Roscoe, which can fight against brain damage (Liu et al., 2020). Radhakrishnan et al. (2014) reported that [6]-Gingerol (5–300 μ M for 72 h) induced apoptosis in SW-480 cells through inhibition of ERK1/2 and JNK, activation of caspase-3-7, and upregulation of cleaved PARP.

The above findings suggest that polyphenols regulate MAPK expression, inhibit cell migration and invasion, induce apoptosis, and inhibit the process of tumor metastasis.

4.5 Alkaloids

Alkaloids are nitrogen-containing alkaline organic metabolites, mainly from plants, animals and fungi, which exhibit a wide range of biological activities: antitumor, antiviral, antimicrobial, anti-inflammatory (Mondal et al., 2019; Abookleesh et al., 2022). The main mechanisms of action of alkaloids include disrupting angiogenesis, blocking EMT, inhibiting cell proliferation, and inducing apoptosis, which have significant therapeutic effects on CRC.

Lycorine, an isoquinoline alkaloid from botanical drug *Lycoria radiata* (L'Hér.) with anti-inflammatory, anticancer, and antiviral effects (Di Sotto et al., 2023). Gao et al. (2021) revealed that Lycorine (0, 5, 10, 20 μ M) increased the level of E-calmodulin, and decreased the expression of N-calmodulin, β -linker, waveform protein, Snail protein, blocking the EMT process, and inhibiting

metastasis and invasion in CT-26, HCT116, and HT-29 cells, which related to the inhibition of MAPK.

Piperlongumine (PPLGM) is an amide alkaloid isolated from *Piper longum* L and serves effectively in anti-proliferative and anti-inflammatory (Thatikonda et al., 2020). Study (Randhawa et al., 2013) showed that PPLGM (0, 10 and 20 μM for 0, 5, 10, 15, 30 min) was able to upregulate the levels of ROS, and activate MEK/ERK pathway, inducing apoptosis in HT-29 cells as manifested by apoptotic vesiculation, chromatin condensation and caspase-3 cleavage.

Matrine (Mat), a tetracyclic quinolizine alkaloid extracted from botanical drug *Sophora flavescens* Aiton, has neuroprotective effects (Chhabra and Mehan, 2023). Du et al. (2023) found that Mat (0, 0.25, 0.5, 1 μM for 24, 48 h) was able to time- and dose-dependently downregulate the phosphorylation levels of JNK and ERK, to decrease the expression of the *Cldn9* gene, to inhibit the formation of VMs, to downregulate N-calmodulin, MMP2, MMP9, resulting in the inhibition of cell proliferation, migration and invasion in CT26 cells.

Homoharringtonine (HHT), a natural alkaloid derived from the *Cephalotaxus hainanensis* H.L.Li, can be used to treat breast cancer (Wang L. B. et al., 2021). Shi et al. (2020) reported that HHT (0.1, 0.2, 0.4, 1.0 μM for 2, 6, 24, 48 h) dose- and time-dependently inhibited EphB4, and downregulated phosphorylation of MEK, ERK1/2, and decreased the expression of Bcl-2, Mcl-1 to promote apoptosis in LoVo cells. Animal experiments showed that HHT (1 mg/kg) inhibited tumor growth in male BALB/C nude mouse.

Tetrandrine is a isoquinoline alkaloid extracted from the botanical drug *Stephania tetrandra* S.Moore with good antibacterial, anti-inflammatory, and anticancer effects (Bhagya and Chandrashekar, 2022). Wu et al. (2010) found that Tetrandrine induced apoptosis by activating P38 MAPK in CT-26 cells.

The above findings suggest that alkaloids can inhibit the EMT process in CRC cells, inhibit invasion and metastasis, block angiogenesis, induce apoptosis, and inhibit tumor growth.

4.6 Other metabolites

Vanillin, a 4 hydroxy 3 methoxybenzaldehyde extracted from the plant *Vanilla pompona* Schiede, could be used to treat inflammation and regenerate intervertebral disc (Zhu et al., 2023b). Li G. et al (2021) found Vanillin (0, 2.5, 3.5 for 48 h) dose-dependently activated ASK1-p38 MAPK pathway and downregulated the expression of NNMT, inducing apoptosis in HT-29 and SW480 cells. *In vivo* experiment showed that, compared with the use of 5-FU alone, the combination of vanillin with 5 Fu has an excellent synergistic effect which could more significantly induce apoptosis and inhibit tumor growth.

Podophyllotoxin (PT), an aryl tetrahydronaphthalene lignan with antiviral effect extracted from the botanical drugs such as *Podophyllum versipelle* Hance (Cui et al., 2020). Lee et al. (2021) demonstrated that PT (0.1, 0.2, 0.3 μM for 24, 48 h) could dose-dependently induce apoptosis and block the cell cycle at G2/M phase in HCT116 cells by increasing the level of ROS, increasing the

phosphorylation of p38 MAPK and upregulating ER stress markers such as RP78, CHOP.

Ursolic acid, a pentacyclic triterpene acid, extracted from botanical drugs such as *Scleromitron diffusum* (Willd.) R.J.Wang and *Prunella vulgaris* L, was used to prevent myocardial ischemic disease (Xu L. L. et al., 2023). Shan et al. (2016) found that Ursolic acid (15, 30, 60 $\mu\text{mol/L}$) dose-dependently downregulated p-MEK1/2, p-ERK1/2, p-p38, p-JNK, and increased cleaved caspase-3, -9, -8, inducing apoptosis in SW620 and RKO cells. What's more, these effects significantly increased when Ursolic acid is used in combination with oxaliplatin.

Di Yu (DY), derived from the botanical drug *Sanguisorba officinalis* L with inhibitory effects on non-small cell lung cancer (Li H. et al., 2022). Zhang et al. (2023) found that 100 $\mu\text{g/mL}$ DY combined with 100 μM 5-FU significantly downregulated the Ras/MEK/ERK pathway, and increased the expression of Bax, cleaved caspase-3, -9, cleaved PARP, enhancing the chemosensitivity to 5-FU, and inhibiting the migration of drug-resistant cells in RKO-R and HCT15-R cells.

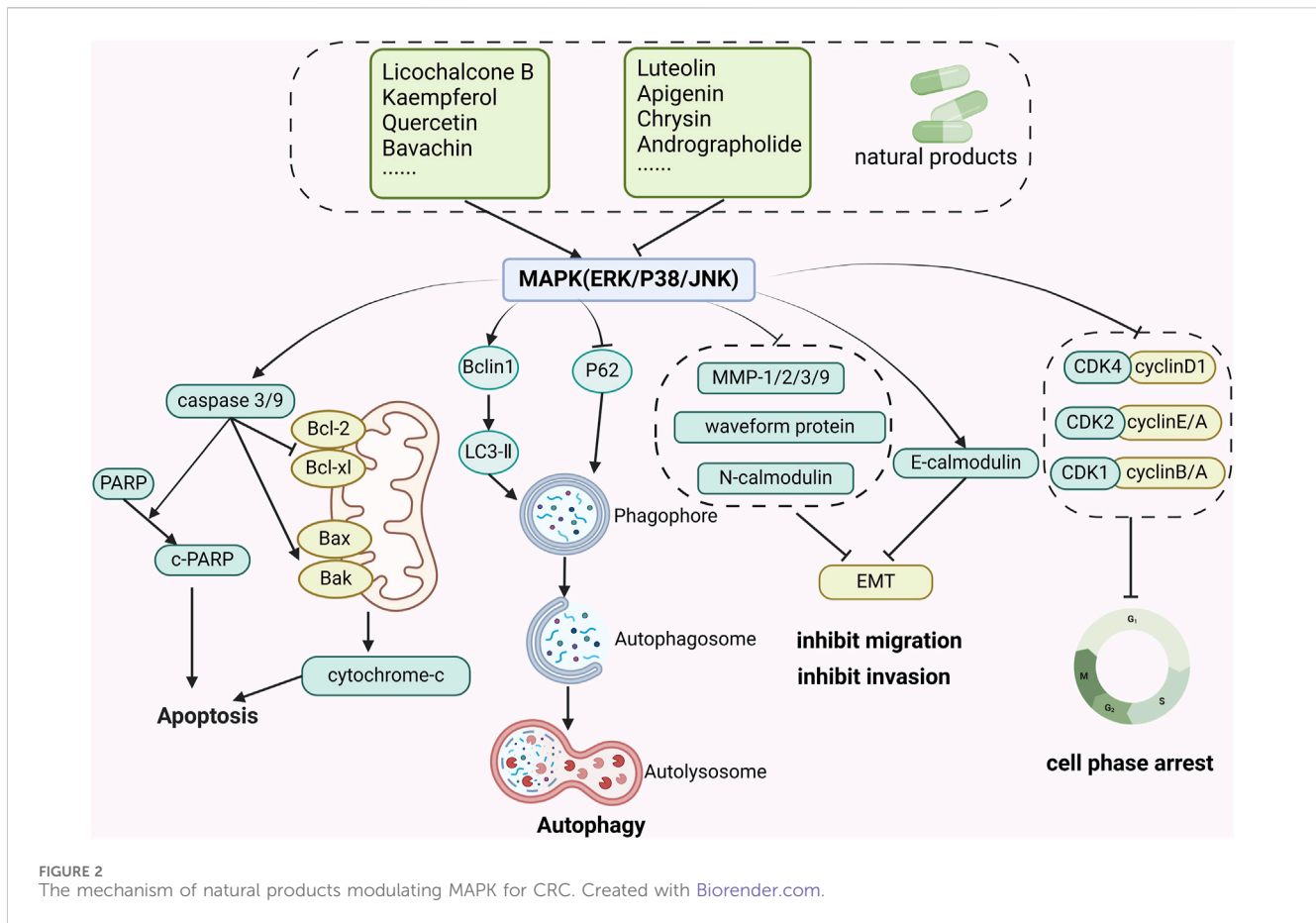
Ferulic acid (FA), a phytophenolic acid found in botanical drug such as *Angelica sinensis* (Oliv.) Diels, has anti-inflammatory, antioxidant properties (Ghasemi-Dehnoo et al., 2023). Chen et al. (2023) reported that FA (20, 40, 80 mg/mL.kg⁻¹ BW for 20 days) could dose-dependently increase the phosphorylation of JNK and ERK, and significantly upregulate the expression of BAX, meanwhile downregulate BCL-2 protein levels in CT26 cell-induced CRC mice. The results indicated that FA inhibit CT26 cell viability and promote apoptosis by upregulating the activities of JNK and ERK.

8-Gingerol is a natural metabolite extracted from *Zingiber officinale* Roscoe that can inhibit excessive autophagy and apoptosis in cardiomyocytes (Xue et al., 2021). It was found that 8-Gingerol (0, 30, 70, and 100 μM) dose-dependently inhibited the EGFR/STAT/ERK pathway and downregulated cyclin D1, c-Myc, and MMP2 expression in HCT116 and DLD1 cells, as well as induced cell cycle arrest in the G0/G1 phase and inhibited cell proliferation and migration. In addition, 8-gingerol can reduce the effective concentration of 5-Fu, thus reducing the toxicity of 5-Fu in drug combination therapy (Hu et al., 2020).

Alantolactone (ALT), a sesquiterpene lactone extracted from *Inula helenium* L, which can be used to fight against liver cancer, lung cancer (Cai et al., 2021). Cao et al. (2019) found that ALT (10 μM) combination with oxaliplatin (40–120 μM) significantly increased ROS level, and upregulated the phosphorylation of JNK and p38 MAPK, inhibiting cell proliferation as well as inducing cell apoptosis in HCT116 and RKO cells. JNK inhibitor SP600125 or p38 inhibitor BMS-582949 could partially reverse the anti-tumor effect.

Curcumin, a guaiacoloid sesquiterpenoid semiketone extracted from the botanical drug *Curcuma longa* L, can be used to alleviate liver fibrosis (Zheng Y. et al., 2022). Wang et al. (2015) reported that Curcuminol (0.05, 0.1, 0.2, 0.4 $\mu\text{M/mL}$ for 24, 48, 72, 96, 120 h) time- and dose-dependently decreased the protein level of IGF-1R, and upregulated the expression of phosphorylated p38, inducing apoptosis in LoVo cells. *In vivo* experiments demonstrated that curcuminol inhibited tumor development.

Salidroside, a glycoside derived from the botanical drug *Rhodiola rosea* L, may improve ameliorate Alzheimer's



disease (Cai et al., 2022). EL-kott et al. (2021) reported that Salidroside showed to be effective in the treatment of HT29 cells by activating protein kinase R, increasing the levels of p-JNK, p38 MAPK, upregulating caspase-3, -8 and inducing apoptosis.

Sulforaphane (SFN), a naturally occurring isothiocyanate widely found in *Brassica oleracea* L, fights against with gastric cancer (Li S. et al., 2022). Sah et al. (2024) found that SFN (1, 2, 5, 10 μ M) dose-dependently reduced ROS and the expression of MAPK, while decreasing the expression of IL-1 β , IL-6 and resulting in inhibition of cell proliferation and invasiveness in HT-29 cells.

Imperatorin, a furanocoumarin extracted from the botanical drug *Angelica dahurica* (Hoffm.) Benth. and Hook.f. ex Franch. and Sav which can inhibit osteosarcoma (Lv et al., 2021). Mi et al. (2017) revealed that Imperatorin (50, 100, 150 μ M) dose-dependently inhibited the phosphorylation of ERK1/2, JNK, p38, disrupted HIF-1 α protein synthesis, and downregulated the expression of VEGF and CD31, inhibiting cell proliferation and angiogenesis, and blocking the cell cycle at G1 phase in HCT116 cells.

Ganoderma lucidum polysaccharide (GLP), a water-soluble polysaccharide extracted from the botanical drug *Ganoderma lucidum* (Curtis) P. Karst, which has antioxidant, anticancer, and neuroprotective effects (Liu X. et al., 2023). Pan. et al. (2019) found that GLP (0, 2.5, 5, 10 mg/mL for 24, 48, 72 h) phosphorylated MAPK/ERK in a dose-dependent manner, and induced the expression of LC3-II, p62, which decreased cellular autophagic

flux and blocked autophagosome-lysosome fusion, inducing apoptosis in HT-29 and HCT116 cells. The above effects were reserved by MAPK/ERK inhibitor PD98059. Animal experiments showed that 300 mg/kg of ALP inhibited tumor growth and autophagic flow in xenografts.

Many experiments have limitations such as short cycles, lack of control groups, and absence of pharmacological toxicity tests. However, considering the limited investment in this field at present, we are lenient about these issues.

In a nut, a large body of evidence suggested that botanical drug extracts (e.g., flavonoids, terpenoids, saponins, polyphenols, alkaloids) could modulate the MAPK pathway, which demonstrated excellent anti-CRC capabilities. The review described mechanisms of natural metabolites in Figure 2.

5 Conclusion

In this review, we summarized the role of the MAPK pathway in the development of CRC from cell growth and proliferation, invasion and migration, apoptosis, autophagy, oxidative stress, pathologic angiogenesis, and chemotherapy resistance, suggesting that the MAPK pathway may be a potential therapeutic target for CRC. We similarly discuss the preventive and therapeutic effects of natural products on CRC by modulating the MAPK pathway. Natural products are characterized by multi-target and multi-pathway collaboration, mainly including flavonoids, terpenoids,

saponins, polyphenols, and alkaloids, etc., and they exhibit adequate anti-metastatic and anti-tumor effects mainly by inhibiting CRC various ways.

At present, the use of natural products to treat diseases has become a trend. Research shows that many natural products have excellent effects due to high safety, multiple targets, rich variety, low toxic and side effects, which have great application potential in the increasingly common diseases. What's more, natural products can inhibit the drug resistance of tumor cells to 5-Fu and OXR. The combination can enhance the drug effects, improve the effectiveness of chemotherapy, alleviate adverse reactions, and overcome drug resistance. However, considering the difficulties in extracting natural products from botanical drugs and their low bioavailability, studies are currently limited to the scope of preclinical experiments, with few studies on CRC patients and a lack of evidence based on high-quality clinical findings. On the one hand, the metabolites of natural products are diverse and often work synergistically, which blocks precise treatment and drug development. On the other hand, considering the requirements of regulations, ethics, the guarantee of safety, and the high research costs, there are currently few clinical trial data. Therefore, we can optimize the research technical routes and methods to quickly and accurately analyze the metabolites and action targets of natural products. At the same time, more animal experiments should be conducted to further study the metabolic process of drug extracts *in vivo*. In addition, potential upstream mechanisms and possible toxicity of natural products need more elucidation.

In conclusion, we reviewed that herbal natural products can prevent and treat CRC by modulating the MAPK signaling pathway, which provides a theoretical basis and new ideas for further exploration of the mechanism of natural metabolites. In order to fully elucidate the preventive and therapeutic effects of natural products on CRC, further studies are needed to illustrate the specific mechanisms involved.

References

- Abokleesh, F. L., Al-Anzi, B. S., and Ullah, A. (2022). Potential antiviral action of alkaloids. *Mol. Basel, Switz.* 27 (3), 903. doi:10.3390/molecules27030903
- Ahmad, M. F., Ahmad, F. A., Khan, M. I., Alsayegh, A. A., Wahab, S., Alam, M. I., et al. (2021). Ganoderma lucidum: a potential source to surmount viral infections through β -glucans immunomodulatory and triterpenoids antiviral properties. *Int. J. Biol. Macromol.* 187, 769–779. doi:10.1016/j.ijbiomac.2021.06.122
- Alotaibi, A. G., Li, J. V., and Gooderham, N. J. (2021). Tumour necrosis factor- α (TNF- α) enhances dietary carcinogen-induced DNA damage in colorectal cancer epithelial cells through activation of JNK signaling pathway. *Toxicology* 457, 152806. doi:10.1016/j.tox.2021.152806
- Asl, E. R., Amini, M., Najafi, S., Mansoori, B., Mokhtarzadeh, A., Mohammadi, A., et al. (2021). Interplay between MAPK/ERK signaling pathway and MicroRNAs: a crucial mechanism regulating cancer cell metabolism and tumor progression. *Life Sci.* 278, 119499. doi:10.1016/j.lfs.2021.119499
- Athamneh, K., Alneyadi, A., Alsamri, H., Alrashedi, A., Palakott, A., El-Tarabily, K. A., et al. (2020). Origanum majorana essential oil triggers p38 MAPK-mediated protective autophagy, apoptosis, and caspase-dependent cleavage of P70S6K in colorectal cancer cells. *Biomolecules* 10 (3), 412. doi:10.3390/biom10030412
- Bailey, C. (2022). Yuanhuacina and related anti-inflammatory and anticancer daphnane diterpenes from genkwa flos-an overview. *Biomolecules* 12 (2), 192. doi:10.3390/biom12020192
- Bhagya, N., and Chandrashekar, K. R. (2022). Autophagy and cancer: can tetrandrine be a potent anticancer drug in the near future? *Biomed. and Pharmacother. = Biomedicine and Pharmacother.* 148, 112727. doi:10.1016/j.biopha.2022.112727
- Bruno, R. M., and Ghiadoni, L. (2018). Polyphenols, antioxidants and the sympathetic nervous system. *Curr. Pharm. Des.* 24 (2), 130–139. doi:10.2174/1381612823666171114170642
- Cai, Y., Chai, Y., Fu, Y., Wang, Y., Zhang, Y., Zhang, X., et al. (2022). Salidroside ameliorates Alzheimer's disease by targeting NLRP3 inflammasome-mediated pyroptosis. *Front. Aging Neurosci.* 13, 809433. doi:10.3389/fnagi.2021.809433
- Cai, Y., Gao, K., Peng, B., Xu, Z., Peng, J., Li, J., et al. (2021). Alantolactone: a natural plant extract as a potential therapeutic agent for cancer. *Front. Pharmacol.* 12, 781033. doi:10.3389/fphar.2021.781033
- Cao, P., Xia, Y., He, W., Zhang, T., Hong, L., Zheng, P., et al. (2019). Enhancement of oxaliplatin-induced colon cancer cell apoptosis by alantolactone, a natural product inducer of ROS. *Int. J. Biol. Sci.* 15 (8), 1676–1684. doi:10.7150/ijbs.35265
- Çetinkaya, M., and Baran, Y. (2023). Therapeutic potential of luteolin on cancer. *Vaccines* 11 (3), 554. doi:10.3390/vaccines11030554
- Chang, L., Zhou, R., He, Y., Meng, M., Hu, J., Liu, Y., et al. (2021). Total saponins from *Rhizoma Panacis Majoris* inhibit proliferation, induce cell cycle arrest and apoptosis and influence MAPK signalling pathways on the colorectal cancer cell. *Mol. Med.* 24 (2), 542. doi:10.3892/mmr.2021.12181
- Chen, L., Jiang, K., Chen, H., Tang, Y., Zhou, X., Tan, Y., et al. (2018). Deguelin induces apoptosis in colorectal cancer cells by activating the p38 MAPK pathway. *Cancer Manag. Res.* 11, 95–105. doi:10.2147/CMARS169476
- Chen, M., Xiao, J., El-Seedi, H. R., Woźniak, K. S., Daglia, M., Little, P. J., et al. (2024). Kaempferol and atherosclerosis: from mechanism to medicine. *Crit. Rev. Food Sci. Nutr.* 64 (8), 2157–2175. doi:10.1080/10408398.2022.2121261

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- Chen, S., Zhao, D., Luan, C., Zheng, J., Liu, W., Feng, Z., et al. (2023). Ferulic acid induces autophagy and apoptosis in colon cancer CT26 cells via the MAPK pathway. *Mol. Basel, Switz.* 28 (16), 6014. doi:10.3390/molecules28166014
- Chhabra, S., and Mehan, S. (2023). Matrine exerts its neuroprotective effects by modulating multiple neuronal pathways. *Metab. Brain Dis.* 38 (5), 1471–1499. doi:10.1007/s11011-023-01214-6
- Choi, J. B., Kim, J. H., Lee, H., Pak, J. N., Shim, B. S., and Kim, S. H. (2018). Reactive oxygen species and p53 mediated activation of p38 and caspases is critically involved in kaempferol induced apoptosis in colorectal cancer cells. *J. Agric. food Chem.* 66 (38), 9960–9967. doi:10.1021/acs.jafc.8b02656
- Cui, Q., Du, R., Liu, M., and Rong, L. (2020). Lignans and their derivatives from plants as antivirals. *Mol. Basel, Switz.* 25 (1), 183. doi:10.3390/molecules25010183
- Debnath, J., Gammoh, N., and Ryan, K. M. (2023). Autophagy and autophagy-related pathways in cancer. *Nat. Rev. Mol. Cell. Biol.* 24 (8), 560–575. doi:10.1038/s41580-023-00585-z
- Di Sotto, A., Valipour, M., Azari, A., Di Giacomo, S., and Irannejad, H. (2023). Benzoindolizidine alkaloids tylophorine and lycorine and their analogues with antiviral, anti-inflammatory, and anticancer properties: promises and challenges. *Biomedicines* 11 (10), 2619. doi:10.3390/biomedicines11102619
- Du, Q., Lin, Y., Ding, C., Wu, L., Xu, Y., and Feng, Q. (2023). Pharmacological activity of matrine in inhibiting colon cancer cells VM formation, proliferation, and invasion by downregulating claudin-9 mediated EMT process and MAPK signaling pathway. *Drug Des. Dev. Ther.* 17, 2787–2804. doi:10.2147/DDDT.S417077
- Ebrahimi, S. O., Reisi, S., and Shareef, S. (2020). miRNAs, oxidative stress, and cancer: a comprehensive and updated review. *J. Cell. physiology* 235 (11), 8812–8825. doi:10.1002/jcp.29724
- El-Kott, A. F., ElBealy, E. R., Alshehri, A. S., El-Kenawy, A. E., Khalifa, H. S., and AlRamlawy, A. M. (2021). Salidroside induces cell apoptosis and inhibits the invasiveness of HT29 colorectal cells by regulating protein kinase R, NF- κ B and STAT3. *Cancer biomarkers Sect. A Dis. markers* 31 (1), 13–25. doi:10.3233/CBM-203257
- Fan, A. H., Zhao, X., Liu, H., Li, D., Guo, T., Zhang, J., et al. (2023). eEF1A1 promotes colorectal cancer progression and predicts poor prognosis of patients. *Cancer Med.* 12 (1), 513–524. doi:10.1002/cam4.4848
- Fang, J. Y., and Richardson, B. C. (2005). The MAPK signalling pathways and colorectal cancer. *Lancet. Oncol.* 6 (5), 322–327. doi:10.1016/S1470-2045(05)70168-6
- Farkhondeh, T., Samarghandian, S., and Roshanravan, B. (2019). Impact of chrysin on the molecular mechanisms underlying diabetic complications. *J. Cell. physiology* 234 (10), 17144–17158. doi:10.1002/jcp.28488
- Gao, F., Yu, X., Li, M., Zhou, L., Liu, W., Li, W., et al. (2020). Deguelin suppresses non-small cell lung cancer by inhibiting EGFR signaling and promoting GSK3 β /FBW7-mediated Mcl-1 destabilization. *Cell. death and Dis.* 11 (2), 143. doi:10.1038/s41419-020-2344-0
- Gao, L., Feng, Y., Ge, C., Xu, X., Wang, S., Li, X., et al. (2021). Identification of molecular anti-metastasis mechanisms of lycorine in colorectal cancer by RNA-seq analysis. *Phytomedicine Int. J. phytotherapy Phytopharm.* 85, 153530. doi:10.1016/j.phymed.2021.153530
- Ghasemi-Dehnoo, M., Amini-Khoei, H., Lorigooini, Z., Anjomshoa, M., and Rafeian-Kopaei, M. (2023). Ferulic acid ameliorates ulcerative colitis in a rat model via the inhibition of two LPS-TLR4-NF- κ B and NF- κ B-INO3-NO signaling pathways and thus alleviating the inflammatory, oxidative and apoptotic conditions in the colon tissue. *Inflammopharmacology* 31 (5), 2587–2597. doi:10.1007/s10787-023-01277-y
- Guesmi, F., Prasad, S., Ali, M. B., Ismail, I. A., and Landoulsi, A. (2021). Thymus hirtus sp. algeriensis Boiss. and Reut. volatile oil enhances TRAIL/Apo2L induced apoptosis and inhibits colon carcinogenesis through upregulation of death receptor pathway. *Aging* 13 (18), 21975–21990. doi:10.18632/aging.203552
- Han, J., Wu, J., and Silke, J. (2020). An overview of mammalian p38 mitogen-activated protein kinases, central regulators of cell stress and receptor signaling. *F1000Research* 9. doi:10.12688/f1000research.22092.1
- Han, S. H., Lee, J. H., Woo, J. S., Jung, G. H., Jung, S. H., Han, E. J., et al. (2024). Platycodin D induces apoptosis via regulating MAPK pathway and promotes autophagy in colon cancer cell. *Biomed. and Pharmacother. = Biomedicine and Pharmacother.* 172, 116216. doi:10.1016/j.biopha.2024.116216
- Hu, S. M., Yao, X. H., Hao, Y. H., Pan, A. H., and Zhou, X. W. (2020). 8-Gingerol regulates colorectal cancer cell proliferation and migration through the EGFR/STAT/ERK pathway. *Int. J. Oncol.* 56 (1), 390–397. doi:10.3892/ijo.2019.4934
- Huang, C., Zhou, T., Ma, L., and Zhao, S. (2023). IFI6 downregulation reverses oxaliplatin resistance of colorectal cancer cells by activating the ROS-induced p38MAPK signaling pathway. *Biol. Pharm. Bull.* 46 (1), 26–34. doi:10.1248/bpb.b22-00439
- Janta, S., Pranweerapaiboon, K., Vivithanaporn, P., Plubrukarn, A., Chairoungdua, A., Prasertsuksri, P., et al. (2023). Holothurin A inhibits RUNX1-enhanced EMT in metastasis prostate cancer via the akt/JNK and P38 MAPK signaling pathway. *Mar. drugs* 21 (6), 345. doi:10.3390/md21060345
- Jenkins, L. J., Luk, I. Y., Fairlie, W. D., Lee, E. F., Palmieri, M., Schoffer, K. L., et al. (2023). Genotype-tailored ERK/MAPK pathway and HDAC inhibition rewire the apoptotic rheostat to trigger colorectal cancer cell death. *Mol. Cancer Ther.* 22 (1), 52–62. doi:10.1158/1535-7163.MCT-22-0101
- Jiang, K., Lu, Q., Li, Q., Ji, Y., Chen, W., and Xue, X. (2017). Astragaloside IV inhibits breast cancer cell invasion by suppressing Vav3 mediated Rac1/MAPK signaling. *Int. Immunopharmacol.* 42, 195–202. doi:10.1016/j.intimp.2016.10.001
- Jiang, X., Li, G., Zhu, B., Zang, J., Lan, T., Jiang, R., et al. (2023). p20BAP31 induces cell apoptosis via both AIF caspase-independent and the ROS/JNK mitochondrial pathway in colorectal cancer. *Cell. and Mol. Biol. Lett.* 28 (1), 25. doi:10.1186/s11658-023-00434-z
- Jin, S., Zhu, T., Deng, S., Li, D., Li, J., Liu, X., et al. (2022b). Dioscin ameliorates cisplatin-induced intestinal toxicity by mitigating oxidative stress and inflammation. *Int. Immunopharmacol.* 111, 109111. doi:10.1016/j.intimp.2022.109111
- Jin, Y., Han, Y., Yang, S., Cao, J., Jiang, M., and Liang, J. (2022a). Endoplasmic reticulum-resident protein Sec62 drives colorectal cancer metastasis via MAPK/ATF2/UC1A1 axis. *Cell. Prolif.* 55 (12), e13253. doi:10.1111/cpr.13253
- Jin, Y., Tangchang, W., Kwon, O. S., Lee, J. Y., Heo, K. S., and Son, H. Y. (2023). Ginsenoside Rh1 ameliorates the asthma and allergic inflammation via inhibiting Akt, MAPK, and NF- κ B signaling pathways *in vitro* and *in vivo*. *Life Sci.* 321, 121607. doi:10.1016/j.lfs.2023.121607
- Kang, K. A., Piao, M. J., Ryu, Y. S., Hyun, Y. J., Park, J. E., Shilnikova, K., et al. (2017). Luteolin induces apoptotic cell death via antioxidant activity in human colon cancer cells. *Int. J. Oncol.* 51 (4), 1169–1178. doi:10.3892/ijo.2017.4091
- Kassasir, H., Papiewska-Pajak, I., Kryczka, J., Boncela, J., and Kowalska, M. A. (2023). Platelet-derived microparticles stimulate the invasiveness of colorectal cancer cells via the p38MAPK-MMP-2/MMP-9 axis. *Cell. Commun. Signal* 21 (1), 51. doi:10.1186/s12964-023-01066-8
- Keil, E., Höcker, R., Schuster, M., Essmann, F., Ueffing, N., Hoffman, B., et al. (2013). Phosphorylation of Atg5 by the Gadd45 β -MEKK4-p38 pathway inhibits autophagy. *Cell. death Differ.* 20 (2), 321–332. doi:10.1038/cdd.2012.129
- Khajeh, E., Rasmi, Y., Kheradmand, F., Malekinejad, H., Aramwit, P., Saboory, E., et al. (2020). Crocetin suppresses the growth and migration in HCT-116 human colorectal cancer cells by activating the p-38 MAPK signaling pathway. *Res. Pharm. Sci.* 15 (6), 592–601. doi:10.4103/1735-5362.301344
- Kim, D. H., Shin, E. A., Kim, B., Shim, B. S., and Kim, S. H. (2018). Reactive oxygen species-mediated phosphorylation of p38 signaling is critically involved in apoptotic effect of Tanshinone I in colon cancer cells. *Phytotherapy Res. PTR* 32 (10), 1975–1982. doi:10.1002/ptr.6126
- Klemke, L., De Oliveira, T., Witt, D., Winkler, N., Bohnenberger, H., Bucala, R., et al. (2021). Hsp90-stabilized MIF supports tumor progression via macrophage recruitment and angiogenesis in colorectal cancer. *Cell. death and Dis.* 12 (2), 155. doi:10.1038/s41419-021-03426-z
- Kwak, A. W., Kim, W. K., Lee, S. O., Yoon, G., Cho, S. S., Kim, K. T., et al. (2023a). Licochalcone B induces ROS-dependent apoptosis in oxaliplatin-resistant colorectal cancer cells via p38/JNK MAPK signaling. *Antioxidants Basel, Switz.* 12 (3), 656. doi:10.3390/antiox12030656
- Kwak, A. W., Lee, J. Y., Lee, S. O., Seo, J. H., Park, J. W., Choi, Y. H., et al. (2023b). Echinatin induces reactive oxygen species-mediated apoptosis via JNK/p38 MAPK signaling pathway in colorectal cancer cells. *Phytotherapy Res. PTR* 37 (2), 563–577. doi:10.1002/ptr.7634
- Kyriakis, J. M., and Avruch, J. (2012). Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. *Physiol. Rev.* 92 (2), 689–737. doi:10.1152/physrev.00028.2011
- Lee, I. G., Lee, J., Hong, S. H., and Seo, Y. J. (2023). Apigenin's therapeutic potential against viral infection. *Front. Biosci. Landmark Ed.* 28 (10), 237. doi:10.31083/fbl2810237
- Lee, S., Rauch, J., and Kolch, W. (2020). Targeting MAPK signaling in cancer: mechanisms of drug resistance and sensitivity. *Int. J. Mol. Sci.* 21 (3), 1102. doi:10.3390/ijms21031102
- Lee, S. O., Joo, S. H., Kwak, A. W., Lee, M. H., Seo, J. H., Cho, S. S., et al. (2021). Podophyllotoxin induces ROS-mediated apoptosis and cell cycle arrest in human colorectal cancer cells via p38 MAPK signaling. *Biomol. and Ther.* 29 (6), 658–666. doi:10.4062/biomolther.2021.143
- Li, F., Huang, T., Tang, Y., Li, Q., Wang, J., Cheng, X., et al. (2021a). Utidelone inhibits growth of colorectal cancer cells through ROS/JNK signaling pathway. *Cell. Death Dis.* 12 (4), 338. doi:10.1038/s41419-021-03619-6
- Li, F., Zhou, Y. D., Liu, J., Cai, J. D., Liao, Z. M., and Chen, G. Q. (2021b). RBP-J promotes cell growth and metastasis through regulating miR-182-5p-mediated Tiam1/Rac1/p38 MAPK axis in colorectal cancer. *Cell. Signal.* 87, 110103. doi:10.1016/j.celsig.2021.110103
- Li, G., Kong, B., Tong, Q., Li, Y., Chen, L., Zeng, J., et al. (2021e). Vanillin downregulates NNMT and attenuates NNMT-related resistance to 5-fluorouracil via ROS-induced cell apoptosis in colorectal cancer cells. *Oncol. Rep.* 45 (6), 110. doi:10.3892/or.2021.8061
- Li, H., Gao, C., Liu, C., Liu, L., Zhuang, J., Yang, J., et al. (2021d). A review of the biological activity and pharmacology of cryptotanshinone, an important active constituent in Danshen. *Biomed. and Pharmacother. = Biomedicine and Pharmacother.* 137, 111332. doi:10.1016/j.biopha.2021.111332
- Li, H., Lin, J., Yang, F., Deng, J., Lai, J., Zeng, J., et al. (2022b). Sanguisorba officinalis L. suppresses non-small cell lung cancer via downregulating the PI3K/AKT/mTOR

- signaling pathway based on network pharmacology and experimental investigation. *Front. Pharmacol.* 13, 1054803. doi:10.3389/fphar.2022.1054803
- Li, Q., Feng, H., Wang, H., Wang, Y., Mou, W., Xu, G., et al. (2022a). Licochalcone B specifically inhibits the NLRP3 inflammasome by disrupting NEK7-NLRP3 interaction. *EMBO Rep.* 23 (2), e53499. doi:10.15252/embr.202153499
- Li, S., Cheng, B., Hou, L., Huang, L., Cui, Y., Xu, D., et al. (2018). Dioscin inhibits colon cancer cells' growth by reactive oxygen species-mediated mitochondrial dysfunction and p38 and JNK pathways. *Anti-cancer drugs* 29 (3), 234–242. doi:10.1097/CAD.0000000000000590
- Li, S., Fu, H., Wang, Y., Wang, L., Jia, B., and Bian, Y. (2020). Curcumin inhibits CT26 cells metastasis by decreasing heparanase expression. *J. Leukoc. Biol.* 108 (6), 1727–1733. doi:10.1002/JLB.1MA0620-357R
- Li, S., Khoi, P. N., Yin, H., Sah, D. K., Kim, N. H., Lian, S., et al. (2022c). Sulforaphane suppresses the nicotine-induced expression of the matrix metalloproteinase-9 via inhibiting ROS-mediated AP-1 and NF- κ B signaling in human gastric cancer cells. *Int. J. Mol. Sci.* 23 (9), 5172. doi:10.3390/ijms23095172
- Li, X., Zhang, C. T., Ma, W., Xie, X., and Huang, Q. (2021c). Oridonin: a review of its pharmacology, pharmacokinetics and toxicity. *Front. Pharmacol.* 12, 645824. doi:10.3389/fphar.2021.645824
- Li, Y., Sun, Y., Fan, L., Zhang, F., Meng, J., Han, J., et al. (2014). Paris saponin VII inhibits growth of colorectal cancer cells through Ras signaling pathway. *Biochem. Pharmacol.* 88 (2), 150–157. doi:10.1016/j.bcp.2014.01.018
- Li, Y., Sun, Y., Tang, T., Niu, Y., Li, X., Xie, M., et al. (2019). Paris saponin VII reverses chemoresistance in breast MCF-7/ADR cells. *J. Ethnopharmacol.* 232, 47–54. doi:10.1016/j.jep.2018.12.018
- Liu, J., Zhang, F., He, J., Wang, S., Wang, L., Li, J., et al. (2023a). Tumor-derived Immunoglobulin-like transcript 4 facilitates angiogenesis of colorectal cancer. *Am. J. Cancer Res.* 13 (2), 419–435.
- Liu, X., Yang, L., Li, G., Jiang, Y., Zhang, G., and Ling, J. (2023c). A novel promising neuroprotective agent: Ganoderma lucidum polysaccharide. *Int. J. Biol. Macromol.* 229, 168–180. doi:10.1016/j.ijbiomac.2022.12.276
- Liu, Y., Deng, S., Zhang, Z., Gu, Y., Xia, S., Bao, X., et al. (2020). 6-Gingerol attenuates microglia-mediated neuroinflammation and ischemic brain injuries through Akt-mTOR-STAT3 signaling pathway. *Eur. J. Pharmacol.* 883, 173294. doi:10.1016/j.ejphar.2020.173294
- Liu, Z., Wang, Z., Zhu, Z., Hong, J., Cui, L., Hao, Y., et al. (2023b). Crocetin regulates functions of neural stem cells to generate new neurons for cerebral ischemia recovery. *Adv. Healthc. Mater.* 12 (20), e2203132. doi:10.1002/adhm.202203132
- Lugano, R., Ramachandran, M., and Dimberg, A. (2020). Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cell. Mol. Life Sci. CMLS* 77 (9), 1745–1770. doi:10.1007/s00018-019-03351-7
- Lv, M., Xu, Q., Zhang, B., Yang, Z., Xie, J., Guo, J., et al. (2021). Imperatorin induces autophagy and G0/G1 phase arrest via PTEN-PI3K-AKT-mTOR/p21 signaling pathway in human osteosarcoma cells *in vitro* and *in vivo*. *Cancer Cell. Int.* 21 (1), 689. doi:10.1186/s12935-021-02397-7
- Lyu, X., Xu, X., Song, A., Guo, J., Zhang, Y., and Zhang, Y. (2019). Ginsenoside Rh1 inhibits colorectal cancer cell migration and invasion *in vitro* and tumor growth *in vivo*. *Oncol. Lett.* 18 (4), 4160–4166. doi:10.3892/ol.2019.10742
- Marchiori, C., Scarpa, M., Kotsafti, A., Morgan, S., Fassan, M., Guzzardo, V., et al. (2019). Epithelial CD80 promotes immune surveillance of colonic preneoplastic lesions and its expression is increased by oxidative stress through STAT3 in colon cancer cells. *J. Exp. and Clin. cancer Res. CR* 38 (1), 190. doi:10.1186/s13046-019-1205-0
- Martin-Vega, A., and Cobb, M. H. (2023). Navigating the ERK1/2 MAPK cascade. *Biomolecules* 13 (10), 1555. doi:10.3390/biom13101555
- Maugeri, A., Calderaro, A., Patanè, G. T., Navarra, M., Barreca, D., Cirmi, S., et al. (2023). Targets involved in the anti-cancer activity of quercetin in breast, colorectal and liver neoplasms. *Int. J. Mol. Sci.* 24 (3), 2952. doi:10.3390/ijms24032952
- Meng, L. Q., Wang, Y., Luo, Y. H., Piao, X. J., Liu, C., Wang, Y., et al. (2018). Quinalizarin induces apoptosis through reactive oxygen species (ROS)-Mediated mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) signaling pathways in colorectal cancer cells. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* 24, 3710–3719. doi:10.12659/MSM.907163
- Mi, C., Ma, J., Wang, K. S., Zuo, H. X., Wang, Z., Li, M. Y., et al. (2017). Imperatorin suppresses proliferation and angiogenesis of human colon cancer cell by targeting HIF-1 α via the mTOR/p70S6K/4E-BP1 and MAPK pathways. *J. Ethnopharmacol.* 203, 27–38. doi:10.1016/j.jep.2017.03.033
- Mo, J. S., Park, W. C., Choi, S. C., Yun, K. J., and Chae, S. C. (2019). MicroRNA 452 regulates cell proliferation, cell migration, and angiogenesis in colorectal cancer by suppressing VEGFA expression. *Cancers* 11 (10), 1613. doi:10.3390/cancers11101613
- Mondal, A., Gandhi, A., Fimognari, C., Atanasov, A. G., and Bishayee, A. (2019). Alkaloids for cancer prevention and therapy: current progress and future perspectives. *Eur. J. Pharmacol.* 858, 172472. doi:10.1016/j.ejphar.2019.172472
- Nam, K. H., and Im, D. S. (2023). Alisol B 23-acetate ameliorates ovalbumin-induced allergic asthma during sensitization and challenge periods. *Biomol. and Ther.* 31 (6), 611–618. doi:10.4062/biomolther.2023.032
- Pan, H., Wang, Y., Na, K., Wang, Y., Wang, L., Li, Z., et al. (2019). Autophagic flux disruption contributes to Ganoderma lucidum polysaccharide-induced apoptosis in human colorectal cancer cells via MAPK/ERK activation. *Cell. death and Dis.* 10 (6), 456. doi:10.1038/s41419-019-1653-7
- Radhakrishnan, E. K., Bava, S. V., Narayanan, S. S., Nath, L. R., Thulasidasan, A. K., Soniya, E. V., et al. (2014). [6]-Gingerol induces caspase-dependent apoptosis and prevents PMA-induced proliferation in colon cancer cells by inhibiting MAPK/AP-1 signaling. *PLoS one* 9 (8), e104401. doi:10.1371/journal.pone.0104401
- Randhawa, H., Kibble, K., Zeng, H., Moyer, M. P., and Reindl, K. M. (2013). Activation of ERK signaling and induction of colon cancer cell death by piperlongumine. *Toxicol. vitro Int. J. Publ. Assoc. BIBRA* 27 (6), 1626–1633. doi:10.1016/j.tiv.2013.04.006
- Ren, C. M., Li, Y., Chen, Q. Z., Zeng, Y. H., Shao, Y., Wu, Q. X., et al. (2016). Oridonin inhibits the proliferation of human colon cancer cells by upregulating BMP7 to activate p38 MAPK. *Oncol. Rep.* 35 (5), 2691–2698. doi:10.3892/or.2016.4654
- Ren, M., Ma, K., Pang, X., Liu, Y., Song, Z., Zhou, R., et al. (2023). Anti-rheumatoid arthritis effects of total saponins from *Rhizoma Panacis Majoris* on adjuvant-induced arthritis in rats and rheumatoid arthritis fibroblast-like synoviocytes. *Phytomedicine Int. J. phytotherapy Phytopharm.* 119, 155021. doi:10.1016/j.phymed.2023.155021
- Rezq, S., Alsemeh, A. E., D'Elia, L., El-Shazly, A. M., Monti, D. M., Sobeh, M., et al. (2020). Thymus algeriensis and Thymus fontanesii exert neuroprotective effect against chronic constriction injury-induced neuropathic pain in rats. *Sci. Rep.* 10 (1), 20559. doi:10.1038/s41598-020-77424-0
- Riahi-Chebbi, I., Souid, S., Othman, H., Haoues, M., Karoui, H., Morel, A., et al. (2019). The Phenolic compound Kaempferol overcomes 5-fluorouracil resistance in human resistant LS174 colon cancer cells. *Sci. Rep.* 9 (1), 195. doi:10.1038/s41598-018-36808-z
- Rozzkowski, S. (2023). Application of polyphenols and flavonoids in oncological therapy. *Mol. Basel, Switz.* 28 (10), 4080. doi:10.3390/molecules28104080
- Sadeghi, M., Dehnavi, S., Asadirad, A., Xu, S., Majeed, M., Jamialahmadi, T., et al. (2023). Curcumin and chemokines: mechanism of action and therapeutic potential in inflammatory diseases. *Inflammopharmacology* 31 (3), 1069–1093. doi:10.1007/s10787-023-01136-w
- Sah, D. K., Arjunan, A., Park, S. Y., Lee, B., and Jung, Y. D. (2024). Sulforaphane inhibits IL-1 β -induced IL-6 by suppressing ROS production, AP-1, and STAT3 in colorectal cancer HT-29 cells. *Antioxidants Basel, Switz.* 13 (4), 406. doi:10.3390/antiox13040406
- Sanz-Ezquerro, J. J., and Cuenda, A. (2021). p38 signalling pathway. *Int. J. Mol. Sci.* 22 (3), 1003. doi:10.3390/ijms22031003
- Schroyer, A. L., Stimes, N. W., Abi Saab, W. F., and Chadee, D. N. (2018). MLK3 phosphorylation by ERK1/2 is required for oxidative stress-induced invasion of colorectal cancer cells. *Oncogene* 37 (8), 1031–1040. doi:10.1038/onc.2017.396
- Shan, J., Xuan, Y., Zhang, Q., Zhu, C., Liu, Z., and Zhang, S. (2016). Ursolic acid synergistically enhances the therapeutic effects of oxaliplatin in colorectal cancer. *Protein and Cell.* 7 (8), 571–585. doi:10.1007/s13238-016-0295-0
- Shi, X., Zhu, M., Gong, Z., Yang, T., Yu, R., Wang, J., et al. (2020). Homoharringtonine suppresses LoVo cell growth by inhibiting EphB4 and the PI3K/AKT and MAPK/ERK1/2 signaling pathways. *Food Chem. Toxicol. Int. J. Publ. Br. Industrial Biol. Res. Assoc.* 136, 110960. doi:10.1016/j.fct.2019.110960
- Siegel, R. L., Giaquinto, A. N., and Jemal, A. (2024). Cancer statistics, 2024. *CA a cancer J. Clin.* 74 (1), 12–49. doi:10.3322/caac.21820
- Silva-Reis, R., Silva, A. M. S., Oliveira, P. A., and Cardoso, S. M. (2023). Antitumor effects of cannabis sativa bioactive compounds on colorectal carcinogenesis. *Biomolecules* 13 (5), 764. doi:10.3390/biom13050764
- Slika, H., Mansour, H., Wehbe, N., Nasser, S. A., Iratni, R., Nasrallah, G., et al. (2022). Therapeutic potential of flavonoids in cancer: ROS-mediated mechanisms. *Biomed. and Pharmacother. = Biomedicine and Pharmacother.* 146, 112442. doi:10.1016/j.biopha.2021.112442
- Song, Y., Bi, Z., Liu, Y., Qin, F., Wei, Y., and Wei, X. (2022a). Targeting RAS-RAF-MEK-ERK signaling pathway in human cancer: current status in clinical trials. *Genes. and Dis.* 10 (1), 76–88. doi:10.1016/j.gendis.2022.05.006
- Song, Y., Yu, J., Li, L., Wang, L., Dong, L., Xi, G., et al. (2022b). Luteolin impacts deoxyribonucleic acid repair by modulating the mitogen-activated protein kinase pathway in colorectal cancer. *Bioengineered* 13 (4), 10998–11011. doi:10.1080/21655979.2022.2066926
- Stramucci, L., and Bossi, G. (2019). Approaching the challenges of MKK3/p38delta MAPK targeting for therapeutic purpose in colorectal cancer. *J. Exp. and Clin. cancer Res. CR* 38 (1), 504. doi:10.1186/s13046-019-1513-4
- Stramucci, L., Pranteda, A., Stravato, A., Amoreo, C. A., Pennetti, A., Diodoro, M. G., et al. (2019). MKK3 sustains cell proliferation and survival through p38DELTA MAPK activation in colorectal cancer. *Cell. death and Dis.* 10 (11), 842. doi:10.1038/s41419-019-2083-2
- Su, M. Q., Zhou, Y. R., Rao, X., Yang, H., Zhuang, X. H., Ke, X. J., et al. (2018). Baicalein induces the apoptosis of HCT116 human colon cancer cells via the upregulation of DEPP/Gadd45a and activation of MAPKs. *Int. J. Oncol.* 53 (2), 750–760. doi:10.3892/ijo.2018.4402
- Suarez-Lopez, L., Kong, Y. W., Sriram, G., Patterson, J. C., Rosenberg, S., Morandell, S., et al. (2021). MAPKAP kinase-2 drives expression of angiogenic factors by tumor-associated macrophages in a model of inflammation-induced colon cancer. *Front. Immunol.* 11, 607891. doi:10.3389/fimmu.2020.607891
- Tai, W. C., Wong, W. Y., Lee, M. M., Chan, B. D., Lu, C., and Hsiao, W. L. (2016). Mechanistic study of the anti-cancer effect of *Gynostemma pentaphyllum* saponins in

- the Apc(Min/+) mouse model. *Proteomics* 16 (10), 1557–1569. doi:10.1002/ptmic.201500293
- Taleb, M. H., Abdeltawab, N. F., Shamma, R. N., Abdelgayed, S. S., Mohamed, S. S., Farag, M. A., et al. (2018). *Origanum vulgare* L. Essential oil as a potential anti-acne topical nanoemulsion *in vitro* and *in vivo* study. *Mol. Basel, Switz.* 23 (9), 2164. doi:10.3390/molecules23092164
- Tam, S. Y., and Law, H. K. (2021). JNK in tumor microenvironment: present findings and challenges in clinical translation. *Cancers* 13 (9), 2196. doi:10.3390/cancers13092196
- Thatikonda, S., Pooladanda, V., Sigalapalli, D. K., and Godugu, C. (2020). Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation via inhibition of hyperproliferation and inflammation. *Cell. death and Dis.* 11 (1), 21. doi:10.1038/s41419-019-2212-y
- Thyagarajan, A., Jedinak, A., Nguyen, H., Terry, C., Baldrige, L. A., Jiang, J., et al. (2010). Triterpenes from *Ganoderma lucidum* induce autophagy in colon cancer through the inhibition of p38 mitogen-activated kinase (p38 MAPK). *Nutr. cancer* 62 (5), 630–640. doi:10.1080/01635580903532390
- Tian, Q., Liu, J., Chen, Q., and Zhang, M. (2023). Andrographolide contributes to the attenuation of cardiac hypertrophy by suppressing endoplasmic reticulum stress. *Pharm. Biol.* 61 (1), 61–68. doi:10.1080/13880209.2022.2157021
- Tong, Q., Qing, Y., Wu, Y., Hu, X., Jiang, L., and Wu, X. (2014). Dioscin inhibits colon tumor growth and tumor angiogenesis through regulating VEGFR2 and AKT/MAPK signaling pathways. *Toxicol. Appl. Pharmacol.* 281 (2), 166–173. doi:10.1016/j.taap.2014.07.026
- Trinh, N. T., Nguyen, T. M. N., Yook, J. I., Ahn, S. G., and Kim, S. A. (2022). Quercetin and quercitrin from *Agrimonia pilosa* Ledeb inhibit the migration and invasion of colon cancer cells through the JNK signaling pathway. *Pharm. Basel, Switz.* 15 (3), 364. doi:10.3390/ph15030364
- Tuli, H. S., Aggarwal, V., Kaur, J., Aggarwal, D., Parashar, G., Parashar, N. C., et al. (2020). Baicalein: a metabolite with promising antineoplastic activity. *Life Sci.* 259, 118183. doi:10.1016/j.lfs.2020.118183
- Ullah, R., Yin, Q., Snell, A. H., and Wan, L. (2022). RAF-MEK-ERK pathway in cancer evolution and treatment. *Seminars cancer Biol.* 85, 123–154. doi:10.1016/j.semcancer.2021.05.010
- Wang, J., Huang, F., Bai, Z., Chi, B., Wu, J., and Chen, X. (2015). Curcumin inhibits growth and induces apoptosis of colorectal cancer LoVo cell line via IGF-1R and p38 MAPK pathway. *Int. J. Mol. Sci.* 16 (8), 19851–19867. doi:10.3390/ijms160819851
- Wang, K., Chen, Q., Shao, Y., Yin, S., Liu, C., Liu, Y., et al. (2021a). Anticancer activities of TCM and their active components against tumor metastasis. *Biomed. and Pharmacother.* = *Biomedicine and Pharmacother.* 133, 111044. doi:10.1016/j.biopha.2020.111044
- Wang, L. B., Wang, D. N., Wu, L. G., Cao, J., Tian, J. H., Liu, R., et al. (2021c). Homoharringtonine inhibited breast cancer cells growth via miR-18a-3p/AKT/mTOR signaling pathway. *Int. J. Biol. Sci.* 17 (4), 995–1009. doi:10.7150/ijbs.44907
- Wang, M., Tian, B., Shen, J., Xu, S., Liu, C., Guan, L., et al. (2023). Bavachin induces apoptosis in colorectal cancer cells through Gadd45a via the MAPK signaling pathway. *Chin. J. Nat. Med.* 21 (1), 36–46. doi:10.1016/S1875-5364(23)60383-8
- Wang, R., Liu, H., Shao, Y., Wang, K., Yin, S., Qiu, Y., et al. (2019). Sophoridine inhibits human colorectal cancer progression via targeting MAPKAPK2. *Mol. cancer Res. MCR* 17 (12), 2469–2479. doi:10.1158/1541-7786.MCR-19-0553
- Wang, Y., Che, J., Zhao, H., Tang, J., and Shi, G. (2018). Platycodin D inhibits oxidative stress and apoptosis in H9c2 cardiomyocytes following hypoxia/reoxygenation injury. *Biochem. biophysical Res. Commun.* 503 (4), 3219–3224. doi:10.1016/j.bbrc.2018.08.129
- Wang, Y., Yang, Z., Wang, Q., Ren, Y., Wang, Q., and Li, Z. (2021b). Bavachin exerted anti-neuroinflammatory effects by regulation of A20 ubiquitin-editing complex. *Int. Immunopharmacol.* 100, 108085. doi:10.1016/j.intimp.2021.108085
- Widmann, C., Gibson, S., Jarpe, M. B., and Johnson, G. L. (1999). Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. *Physiol. Rev.* 79 (1), 143–180. doi:10.1152/physrev.1999.79.1.143
- Wu, J. M., Chen, Y., Chen, J. C., Lin, T. Y., and Tseng, S. H. (2010). Tetrandrine induces apoptosis and growth suppression of colon cancer cells in mice. *Cancer Lett.* 287 (2), 187–195. doi:10.1016/j.canlet.2009.06.009
- Wu, Q., Wu, W., Fu, B., Shi, L., Wang, X., and Kuca, K. (2019). JNK signaling in cancer cell survival. *Med. Res. Rev.* 39 (6), 2082–2104. doi:10.1002/med.21574
- Wu, Q. B., Chen, J., Zhu, J. W., Yin, X., You, H. Y., Lin, Y. R., et al. (2018). MicroRNA-125 inhibits RKO colorectal cancer cell growth by targeting VEGF. *Int. J. Mol. Med.* 42 (1), 665–673. doi:10.3892/ijmm.2018.3632
- Xie, P., Luo, H. T., Pei, W. J., Xiao, M. Y., Li, F. F., Gu, Y. L., et al. (2024). Saponins derived from *Gynostemma pentaphyllum* regulate triglyceride and cholesterol metabolism and the mechanisms: a review. *J. Ethnopharmacol.* 319 (Pt 1), 117186. doi:10.1016/j.jep.2023.117186
- Xu, G., Fu, S., Zhan, X., Wang, Z., Zhang, P., Shi, W., et al. (2021). Echinatin effectively protects against NLRP3 inflammasome-driven diseases by targeting HSP90. *JCI insight* 6 (2), e134601. doi:10.1172/jci.insight.134601
- Xu, G., Zhao, L., Hua, Q., Wang, L., Liu, H., Lin, Z., et al. (2023a). CEMIP, acting as a scaffold protein for bridging GRAF1 and MIB1, promotes colorectal cancer metastasis via activating CDC42/MAPK pathway. *Cell. death and Dis.* 14 (2), 167. doi:10.1038/s41419-023-05644-z
- Xu, L. L., Su, H. X., Li, P. B., and Li, H. H. (2023b). Ursolic acid ameliorates myocardial ischemia/reperfusion injury by improving mitochondrial function via immunoproteasome-pp2a-AMPK signalling. *Nutrients* 15 (4), 1049. doi:10.3390/nu15041049
- Xu, Z., Jiang, H., Zhu, Y., Wang, H., Jiang, J., Chen, L., et al. (2017). Cryptotanshinone induces ROS-dependent autophagy in multidrug-resistant colon cancer cells. *Chemico-biological Interact.* 273, 48–55. doi:10.1016/j.cbi.2017.06.003
- Xue, Y., Zhang, M., Liu, M., Liu, Y., Li, L., Han, X., et al. (2021). 8-Gingerol ameliorates myocardial fibrosis by attenuating reactive oxygen species, apoptosis, and autophagy via the PI3K/Akt/mTOR signaling pathway. *Front. Pharmacol.* 12, 711701. doi:10.3389/fphar.2021.711701
- Ye, B., Qiao, K., Zhao, Q., Jiang, Z., Hu, N., and Wang, F. (2022). Tanshinone I restrains osteosarcoma progression by regulating circ_0000376/miR-432-5p/BCL2 axis. *Mol. Cell. Biochem.* 477 (1), 1–13. doi:10.1007/s11010-021-04257-4
- Yuan, M., Meng, W., Liao, W., and Lian, S. (2018). Andrographolide antagonizes TNF- α -Induced IL-8 via inhibition of NADPH oxidase/ROS/NF- κ B and src/MAPKs/AP-1 Axis in human colorectal cancer HCT116 cells. *J. Agric. food Chem.* 66 (20), 5139–5148. doi:10.1021/acs.jafc.8b00810
- Zhang, R., Wang, Y., Li, J., Jin, H., Song, S., and Huang, C. (2014). The Chinese herb isolate yuanhuacine (YHL-14) induces G2/M arrest in human cancer cells by up-regulating p21 protein expression through an p53 protein-independent cascade. *J. Biol. Chem.* 289 (10), 6394–6403. doi:10.1074/jbc.M113.513960
- Zhang, W., Ou, L., Peng, C., Sang, S., Feng, Z., Zou, Y., et al. (2023). Sanguisorba officinalis L. enhances the 5-fluorouracil sensitivity and overcomes chemoresistance in 5-fluorouracil-resistant colorectal cancer cells via Ras/MEK/ERK and PI3K/Akt pathways. *Heliyon* 9 (6), e16798. doi:10.1016/j.heliyon.2023.e16798
- Zhang, X., Zhang, W., Chen, F., and Lu, Z. (2021). Combined effect of chrysin and apigenin on inhibiting the development and progression of colorectal cancer by suppressing the activity of P38-MAPK/AKT pathway. *IUBMB life* 73 (5), 774–783. doi:10.1002/iub.2456
- Zhao, J., Ou, B., Han, D., Wang, P., Zong, Y., Zhu, C., et al. (2017). Tumor-derived CXCL5 promotes human colorectal cancer metastasis through activation of the ERK/Elk-1/Snail and AKT/GSK3 β /catenin pathways. *Mol. Cancer* 16 (1), 70. doi:10.1186/s12943-017-0629-4
- Zheng, X., Wei, J., Li, W., Li, X., Wang, W., Guo, J., et al. (2020). PRDX2 removal inhibits the cell cycle and autophagy in colorectal cancer cells. *Aging* 12 (16), 16390–16409. doi:10.18632/aging.103690
- Zheng, Y., Zhao, T., Wang, J., Jiang, R., Huang, J., Li, W., et al. (2022b). Curcumin alleviates liver fibrosis through inducing autophagy and ferroptosis in hepatic stellate cells. *FASEB J. official Publ. Fed. Am. Soc. Exp. Biol.* 36 (12), e22665. doi:10.1096/fj.202200933RR
- Zheng, Z., Zhang, L., and Hou, X. (2022a). Potential roles and molecular mechanisms of phytochemicals against cancer. *Food and Funct.* 13 (18), 9208–9225. doi:10.1039/d2fo1663j
- Zhu, H. C., Jia, X. K., Fan, Y., Xu, S. H., Li, X. Y., Huang, M. Q., et al. (2021). Alisol B 23-acetate ameliorates azoxymethane/dextran sodium sulfate-induced male murine colitis-associated colorectal cancer via modulating the composition of gut microbiota and improving intestinal barrier. *Front. Cell. Infect. Microbiol.* 11, 640225. doi:10.3389/fcimb.2021.640225
- Zhu, Z., Guo, Y., Liu, Y., Ding, R., Huang, Z., Yu, W., et al. (2023a). ELK4 promotes colorectal cancer progression by activating the neoangiogenic factor LRG1 in a noncanonical SP1/3-dependent manner. *Adv. Sci. Weinheim, Baden-Wuerttemberg, Ger.* 10 (32), e2303378. doi:10.1002/advs.202303378
- Zhu, Z., Yu, Q., Li, H., Han, F., Guo, Q., Sun, H., et al. (2023b). Vanillin-based functionalization strategy to construct multifunctional microspheres for treating inflammation and regenerating intervertebral disc. *Bioact. Mater.* 28, 167–182. doi:10.1016/j.bioactmat.2023.05.005

Glossary

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| CRC | Colorectal cancer |
| MAPK | Mitogen-activated protein kinase |
| AS-IV | Astragaloside IV |
| HA | Holothurin A |
| ERK | extracellular regulating kinase |
| p38 MAPK | p38 mitogen-activated protein kinase |
| JNK | Jun N-terminal kinase |
| RAS | Ras small GTPase |
| EGFR | epidermal factor receptor |
| PAMPs | Pathogen-Associated Molecular Patterns |
| DAMPs | Danger-Associated Molecular Patterns |
| eEF1A1 | Eukaryotic elongation factor 1 A1 |
| ROS | reactive oxygen species |
| MIF | migration inhibitory factor |
| ILT4 | Immunoglobulin-like transcript 4 |
| LCB | Licochalcone B |
| Bcl-2 | B-cell lymphoma-2 |
| LC3II | light chain 3 II |
| LC3I | light chain 3 I |
| Ech | Echinatin |
| OME0 | Origanum majoana Essential Oil |
| Tan I | Tanshinone I |
| ORI | Oridonin |
| CTS | Cryptotanshinone |
| AB23A | Alisol B 23-acetate |
| GLT | Ganoderma lucidum triterpenes |
| RPMTG | Rhizoma Panacis Majoris |
| PD | Platycodin D |
| GpS | Gynostemma pentaphyllum saponins |
| PPLGM | Piperlongumine |
| FA | Ferulic acid |
| GLP | Ganoderma lucidum polysaccharide |
| TNF-α | tumor necrosis factor- α |
| NF-κB | Nuclear factor kappa- β |