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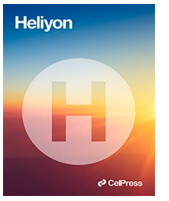

Review article

Progress on the mechanism of action of emodin against breast cancer cells

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ABSTRACT

At present, the role of active ingredients of traditional Chinese medicine in tumor therapy has gradually attracted people's attention, and anthraquinones, which are structurally similar to adriamycin and epirubicin, are one of the hotspots of research. Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is a natural anthraquinone compound isolated from rhubarb, Polygonum cuspidatum, and aloe vera. In recent years, emodin has received widespread attention for its remarkable anti-tumor effects, and its anti-breast cancer effects are manifested as induction of apoptosis, inhibition of tumor cell proliferation, inhibition of invasion and metastasis of tumor cells, and anti-tumor drug resistance. Moreover, emodin can act against multiple types of breast cancer cells by acting on different targets. In this paper, we reviewed the latest research progress on the anti-breast cancer effects of emodin and its anti-tumor mechanism, to provide reference and information for the treatment of breast cancer and the development of anti-tumor drugs.

ENGLISH ABBREVIATION TABLE

ABBREVIATIONS	FULL TITLE IN ENGLISH
EM	Emodin
BCa	Breast cancer
HER-2	Human epidermal growth factor
ER	Estrogen receptor
PR	Progesterone receptor
TNBC	Triple-negative breast cancer
TCM	Traditional Chinese medicine
SAC	Spindle attachment checkpoint
CCL5	chemokine (C-C motif) ligand 5
EMT	epithelial-mesenchymal transition
AhR	aryl hydrocarbon receptor

(*continued on next page*)

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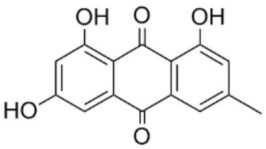
(*continued*)

PERK	protein kinase R-like endoplasmic reticulum kinase
TAMs	tumor-associated macrophages
TME	tumor microenvironment
TFH	Thin-film hydration
DOX	doxorubicin
MDR	multidrug resistance
MLE	multi-component magnetic liposomal emodin capsule
5-FU	5-fluorouracil
TQ	Thymoquinone
EG	emodin-8-O-β-D glucoside
PTX	paclitaxel



1. Introduction

Breast cancer (BCa) is a major health problem for women worldwide [1].In recent years, breast cancer has been recognized as a series of diseases with distinct pathologies, molecular structures, and clinical

Features [2].These diseases have different presentations, morphology, biology and clinical subtypes [3]. The classification of breast cancer subtypes has been evolving, and the generally acceptable classification is based on an immunologic perspective that divides breast cancer into four subtypes: luminal A, luminal B, HER2-positive, and triple-negative, based on estrogen (ER), progesterone (PR), and human epidermal growth factor (HER2) [4].Depending on the type of breast cancer, different types of medications are needed. For patients with HER2-positive breast cancer, trastuzumab, a HER2-specific monoclonal antibody, can be used to improve the survival rate of patients with early-stage breast cancer [5].Endocrine therapy with aromatase inhibitors can be used in patients with ER or PR-positive breast cancer, but prescription tamoxifen can also be used if there are cases of intolerance to inhibitors or if there is a risk of osteoporosis [6].Finally, triple-negative breast cancer (TNBC) is often treated with chemotherapy. (see Table 1, Figs. 1-5)

Compared with traditional chemotherapeutic drugs, traditional Chinese medicine (TCM) have some unique advantages in modern medicine, such as low price, low toxicity and side effects, easy to be accepted by patients, etc. In the clinical basic experiments, some TCM ingredients have also verified that they can effectively intervene in breast cancer cells [7].Therefore, emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) extracted from rhubarb, semen cassiae, and Polygonum multiflorum and other traditional Chinese medicines, as a tyrosine protein kinase inhibitor and an anticancer drug, is similar to the commonly used chemotherapeutic drugs for breast cancer, mitoxantrone and adriamycin, which have an anthraquinone structure. A large number of studies have shown that emodin has inhibitory effects on a variety of tumor cells, including lung cancer, breast cancer, liver cancer and ovarian cancer cells [8].Therefore, this paper explores the potential significance of emodin in breast cancer treatment from the perspective of antitumor mechanism.

Emodin is a broad-spectrum anticancer agent.To the best of our knowledge, it may be harmful by inhalation causing respiratory irritation, and is harmful if ingested or taken and may cause skin irritation if absorbed through the skin.

The 1 % component has been identified by IARC as a probable or definite human carcinogen. The chemical, physical and toxicological properties have not been fully investigated.

Table 1
y, triple-negative breast cancer (TNBC).

Drug Combination	Possible mechanisms	Targets	Reference
Emodin+5-fluorouracil	Apoptosis	NRARP	13,40
Emodin + thymoquinone	Proliferation、Migration	NA	38,41
Emodin + Tamoxifen	Overexpression	CyclinD1 P-ERK	42,43
Emodin + Curcumin	Proliferation, Migration、Apoptosis	MiR-34	44,45
Emodin + Berberine	Proliferation, Migration, Apoptosis	SIK3	46,47,48
		mTOR	
		Akt	
Possible mechanisms	Real Modules (animals/cell)	Targets	Reference
Apotosis	MCF-7	FASL、MCL1、CCND1、C-MYC	10,11
	MCF-7	AhR-CYP1A1	12
Proliferation	MCF-7	PI3K、AKT、BCL-2、cyclinD1	18,19
	MDA-MB-453	HER-2	22,23
	4T1	M2 polarization	19
Invasion	TNBC	CCL5	24,25
	MDA-MB-435	NF-κB、ATP、P2X7	26,27
	Macrophages	TGF-β1、P2X7、EMT	28,29,30

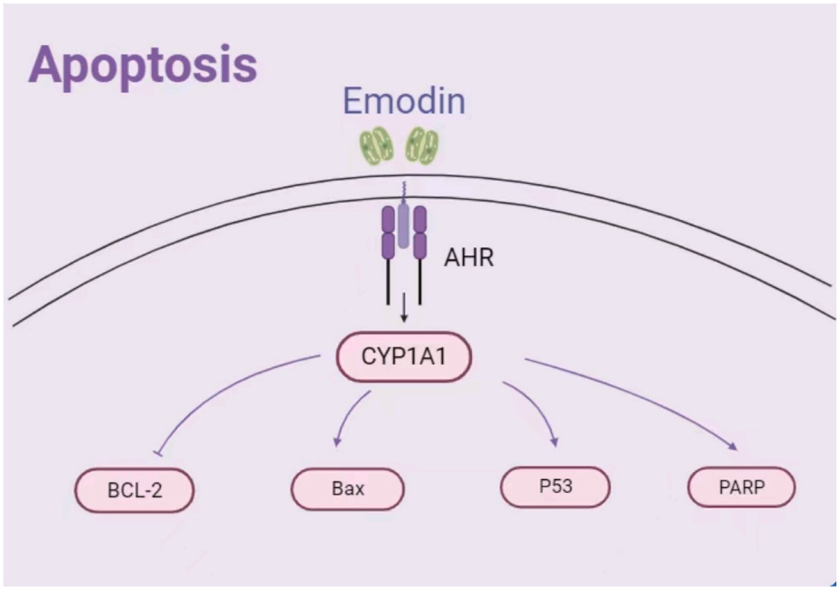


Fig. 1. Mechanism of emodin inducing apoptosis in breast cancer.

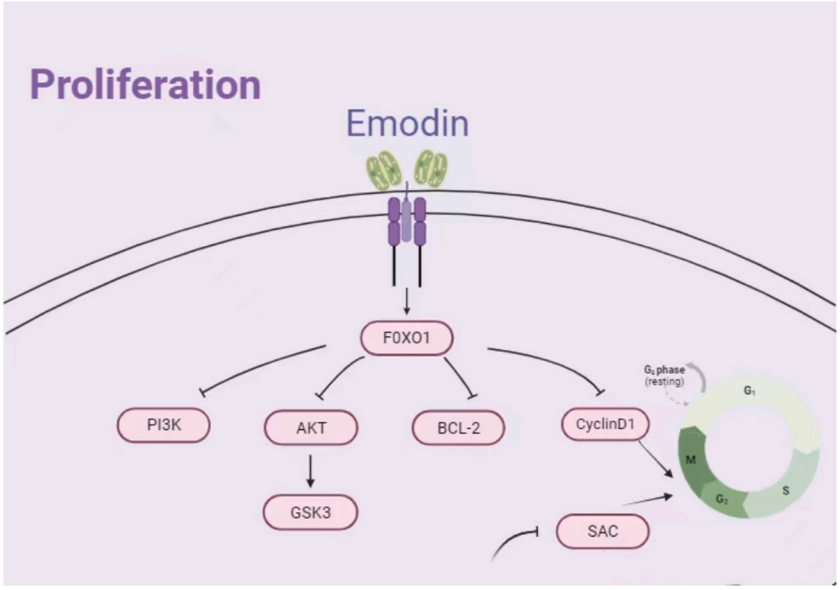


Fig. 2. Mechanism of emodin suppressing proliferation in breast cancer.

2. Anti-breast cancer mechanism of emodin

2.1. Promote apoptosis of breast cancer cells

Apoptosis is a non-lytic form of cell death that can be induced by a variety of stimuli, including physiological and pathologic factors. In general, apoptosis affects tumor formation and progression through intrinsic or extrinsic pathways [9].It has been suggested that an important hallmark of cancer is the disruption of the apoptotic mechanism, therefore, induction of apoptosis is an important strategy for anti-tumor therapy [10].Emodin has pro-apoptotic effects on both ER(−) and ER(+) breast cancer cells. For example, Wing-Yan et al. found that emodin could induce growth inhibition and apoptosis in breast cancer MCF-7 cells (ER+) by regulating the expression of apoptosis-related genes, such as FASL, MCL1, CCND1, and C-MYC, and the mechanism may be related to the promotion of intrinsic and extrinsic apoptotic pathways and inducing cell cycle arrest [11].NingZhang et al. further found that emodin is a potent aryl hydrocarbon receptor (AhR) agonist, and emodin may exert its inhibitory effect on MCF-7 cells by activating the AhR-CYP1A1

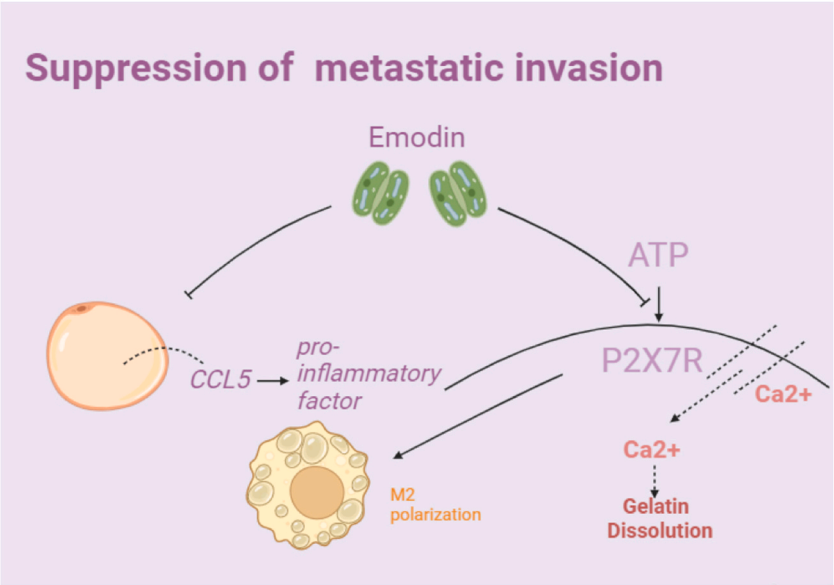


Fig. 3. Mechanism of emodin suppressing metastasis and invasion in breast cancer.

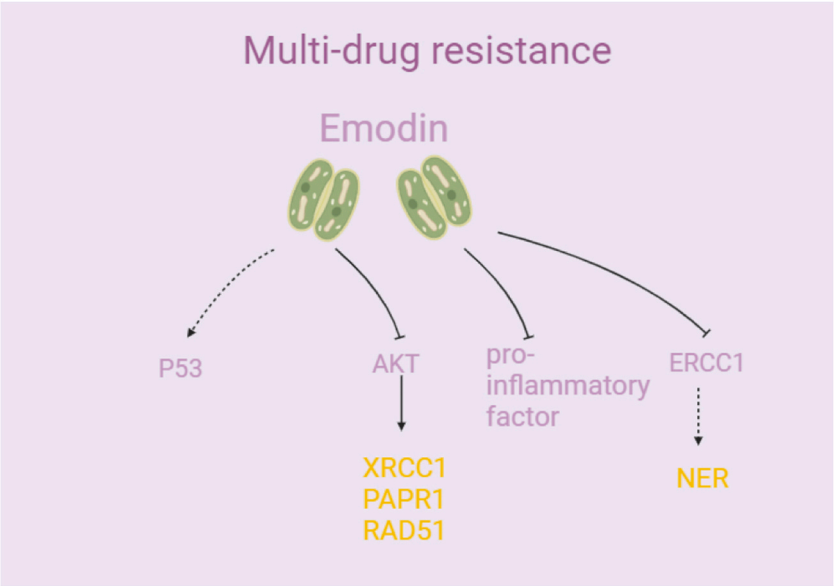


Fig. 4. Mechanism of emodin's multi-drug resistance in breast cancer.

signaling pathway [12].Several studies have found that treatment of breast cancer cells Bcap-37 (ER+) and ZR-75-30 (ER(+); PR(−); HER2(+)) with emodin greatly reduced levels of Bcl-2 and increased the levels of c-casp3, PARP, p53, and Bax, and that its inhibitory growth and apoptosis-inducing effects were time- and dose-dependent [13,14].

2.2. Inhibition of tumor cell proliferation

Cell proliferation is the most common cellular biological feature, and malignant proliferation generally occurs in tumor tissue cells, e.g., the rate of proliferation is significantly increased and the proteins that regulate proliferation are altered [15].In addition, the cell cycle is a fundamental process of life activity, and cell cycle dysregulation leading to unrestricted cell proliferation is one of the important factors in tumorigenesis [16].Studies have demonstrated that emodin has good anti-tumor proliferation activity against ER+ and ER-breast cancer tumor cells. The inhibitory effect on ER + breast cancer was particularly pronounced [17].

Early studies have found that emodin blocks estrogen-induced ERα expression, which in turn down-regulated the expression of its

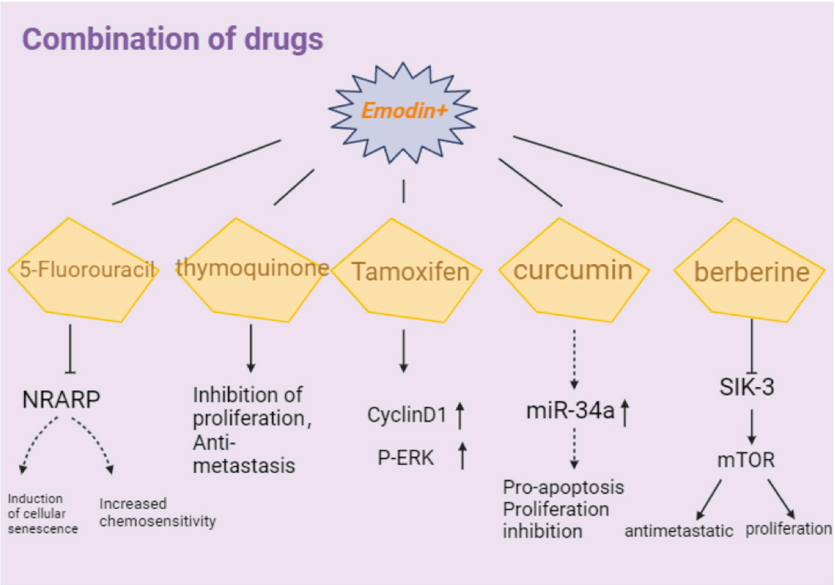


Fig. 5. Mechanism of emodin's combination of drugs in breast cancer.

downstream proteins, cyclin D1 and Bcl-2 protein, to exert tumor suppression, and also exerted an inhibitory effect on ER+ and ER- breast cancer tumors by decreasing the expression of PI3K/Akt protein [18]. Sakalli-Tecim et al. obtained similar conclusions through bioinformatics analysis and further suggested that FOXO1 plays a key signaling molecule role in the proliferation of ER(+) breast cancer cells, and that emodin intervention in MCF-7 cells could promote FOXO1 expression while inhibiting the expression of PI3K, AKT, BCL-2, and cyclinD1. Spindle attachment checkpoint (SAC) may be a key target for emodin intervention in triple-negative breast cancer [19].

Due to the poor oral utilization of emodin, it may only have an inhibitory effect on early-stage tumors, with poor direct toxicity on advanced tumors or areas with poor blood supply, and its antitumor effects may be related to the tumor microenvironment. Song et al. suggested that emodin can inhibit triple-negative breast cancer cells by inhibiting adipocyte secretion of CCL5 (chemokine (C-C motif) ligand 5) and thus inhibiting AKT expression, promoting GSK3 activation, which in turn inhibits the expression of epithelial-mesenchymal transition and invasion-related markers (waveform protein, snail, (MMP)-2 and MMP-9) [17]. Studies have shown that emodin can exert tyrosine kinase inhibition by preventing the binding of tyrosine kinase to ATP [20,21]. When HER-2 is over-expressed and activating mutations, it increases intracellular tyrosine kinase expression. Therefore, using HER-2 overexpressed breast cancer cells MDA-MB-453, one study found that emodin and emodin derivative DK-V-47 significantly inhibited tyrosine kinase activity in HER-2 overexpressed breast cancer cells, which in turn inhibited proliferation and metastasis of tumor cells [22].Stephen Iwanowycz et al. [23] Performed in vitro experiments using triple-negative breast cancer 4T1 cells and murine-derived breast cancer cells, and found that the antitumor effects of emodin may be related to the tumor microenvironment. Other experiment results suggest that emodin can inhibit tumor growth by inhibiting macrophage infiltration and M2 polarization, increasing T-cell activation and decreasing tumor angiogenesis, as well as blocking feed-forward loops between breast cancer cells and tumor-associated macrophages (TAMs). Sakalli-Tecim [19]et al. provide data further suggesting that rhodopsin may affect breast cancer growth by modulating the tumor microenvironment (TME). In clinical therapy then, if administered at an early stage of cancer development, emodin may be most effective in treating early-stage breast cancer or inhibiting tumor recurrence or metastasis after surgical removal of the primary tumor.

2.3. Inhibition of tumor cell metastasis and invasion

Cancer metastasis is the result of a combination of tumor cells and tumor microenvironment cells [24].Inhibition of tumor cell metastasis plays a crucial role in cancer therapy [25].SONG et al. [17]found that emodin inhibited the secretion of CCL5 from adipocytes, and suppressed tumor growth and metastasis by inhibiting EMT of TNBC cells, indicating that emodin has a novel role in preventing the metastasis of TNBC, and it is a promising research prospect as a novel therapeutic drug for preventing TNBC. Not only that, Abdellatef et al. [26] found that emodin was able to control the migration and invasive ability of TNBC by inhibiting NF-κB activity and the expression of its downstream target molecules. Bilel Jelassi et al. Suggested that emodin might be effective in inhibiting human breast cancer invasion by inhibiting P2X7. 1 μM and 10 μM emodin elevated ATP-induced intracellular Ca^{2+} concentration by 35 % and 60 %,respectively. Emodin specifically inhibited P2X7-mediated calcium efflux with an IC50 of 3 μM. At low concentrations (<10 μM), emodin had little effect on the activity of breast cancer cells but significantly reduced the invasion of P2X7-positive breast cancer cells, such as MDA-MB-435 cells (highly metastatic cells of human breast cancer) by a mechanism-related to the prevention of the increase in ATP-induced gelatinolytic activity. However, it had no effect on P2X7-negative MDA-MB-468 cells

[27]. Previously, it was found that emodin antagonizes the P2X7 on macrophages in colon cancer, thereby inhibiting macrophage M2-type polarization and suppressing the inflammatory response [28]. Recently, it has also been shown in TNBC, that emodin also interferes with breast cancer cells and macrophages via the P2X7, thereby inhibiting systemic inflammatory responses and reducing systemic and tumor-local M2-type macrophages, thus inhibiting BC metastasis to the lungs [29]. It has also been shown that TGF-β1 secreted by macrophages can influence breast cancer cells to undergo EMT through autocrine and paracrine effects. It is evident that emodin inhibits EMT and reduces the number of CSC/TIC in breast cancer cells by blocking TGF-β1-mediated interaction between macrophages and breast cancer cells. Moreover, the brief use of emodin before surgery can significantly reduce the recurrence of lung metastasis of breast cancer after surgery [30].

3. Reversal of multidrug resistance in breast cancer

The mainstay of breast cancer treatment is chemotherapy, but its major limiting factor is multidrug resistance, which can lead to inactivation of chemotherapeutic agents and a mortality rate capable of exceeding 90 %, and multidrug resistance is mainly caused by the overexpression of drug transporters and related enzymes in breast cancer cells [31,32].Drug resistance in HER2-positive breast cancer is associated with mutations. PI3KCA-activating mutations are present in about 20–30 % of patients, which in turn mediate trastuzumab resistance.TNBC usually have genetic abnormalities associated with drug resistance. Therefore, the mechanism of breast cancer drug resistance involves metabolic reprogramming, altered DNA damage repair mechanisms, and inflammatory responses of ERCC1 overexpression can lead to multidrug resistance to chemotherapy in cancer treatment. ERCC1 is a DNA damage repair gene, and NRCC1 is a key enzyme for tumor cell NER in radiotherapy-induced DNA damage.Fu et al. showed in vitro that emodin down-regulated ERCC1 protein expression and reversed multidrug resistance in MCF-7/Adr cells, but ERCC1 plays a specific role in reversing drug resistance needs to be further investigated [33]. In addition, Kim et al. found that doxorubicin (DOX) is a cytotoxic drug for the treatment of breast cancer, but its multidrug resistance (MDR) affects its application in the clinic [34,35]. Subsequently, Li et al. investigated the role of emodin in breast cancer against DOX resistance, and showed that emodin could inhibit BC cell proliferation by regulating the AKT1/PI3K/mTOR signaling pathway, which in turn increase the sensitivity of BC cells to DOX, and reverse the development of their resistance to DOX [36].Inflammatory response also plays a role in promoting multidrug resistance in breast cancer, and emodin may also play a role in combating multidrug resistance in BCa by inhibiting inflammatory response, but the exact mechanism remains to be investigated.

4. New dosage forms

Liposomes have good biocompatibility and stability and can effectively encapsulate lipophilic and hydrophilic molecules [37]. Liposomes have become a major material for drug delivery therapy, and in clinical applications, liposomes can attenuate off-target toxicity of various drugs, and promote transportation in blood circulation as well as diffuse distribution of drug distribution, thus improving clinical efficacy [38].Although emodin has a wide range of pharmacological activities, it also has limitations such as low oral utilization and poor solubility, which greatly restrict its clinical application in the treatment of breast cancer. Therefore, SONG et al. designed and manufactured a multi-component magnetic liposomal emodin capsule (MLE), which adopts the Thin-film hydration (TFH) method to better disperse the molecules with high magnetic properties in aqueous solution, enhance the specific targeting effect and greatly improve the chemotherapeutic effect on breast cancer cells. In addition, the excellent magnetic resonance properties of this compound can be used to observe and judge the magnetic field-directed aggregation within tumors to facilitate clinical diagnosis and treatment [39].

The poor pharmacokinetic parameters of emodin, as well as its very low water solubility and high permeability, greatly limit its clinical application.In order to enhance the antitumor activity, Tuli HS et al. investigated nanotechnology drug carriers such as nanoparticles, nanofibers, nano-transfers, and nanoemulsions in order to increase sustained drug release of emodin, thereby increasing the availability and duration of action of the drug.These results suggest that as nanotechnology-mediated drug delivery can offer promising potential applications in cancer therapy, in addition, this novel form of drug delivery may be a promising approach for cancer treatment.

5. Combination of drugs

The combination of antitumor drugs is now a new trend in cancer treatment, where the combined use of antitumor drugs from the point of view of the action target, drug sensitivity, and cell cycle proliferation may provide a multiplier effect. It has been demonstrated that survival time can be prolonged and the chance of single-drug resistance can be reduced by the combination of different drugs [40]. A rational combination of therapeutic agents based on the disease spectrum will provide the greatest benefit to BC patients [41].In terms of combination therapies, it can be divided into two main categories: combination with chemotherapeutic agents and combination with active derivatives.

5.1. Chemotherapy treatment

First, 5-fluorouracil (5-FU)resistance is a major obstacle in the treatment of malignant tumors, Zu et al. found that emodin can reverse its 5-Fu resistance through the PI3K/Akt signaling pathway [13].The data suggest that a regimen combining emodin with 5-FU not only silences NRARP, but also induces tumor cell senescence, thereby significantly enhancing the efficacy of cancer chemotherapy

[42]. The combination therapy of thymoquinone and emodin synergistically enhances breast cancer cell apoptosis, inhibits cell migration, and effectively reduces stem cell rate [40]. Thymoquinone (TQ; 2-isopropyl-5-methylbenzo-1,4-quinone) is the main active ingredient of black asclepiad and has shown favorable therapeutic efficacy in many studies [43]. The combination of tamoxifen and emodin can limit the growth and migration of MCF-7 breast cancer cells, inhibit the growth of breast cancer stem cells, and reverse chemoresistance while reducing systemic toxicity [40].Tamoxifen is the most commonly used drug for the treatment of ER(+) breast cancer [44]. Kim et al. found that the combination of tamoxifen and emodin antagonized the overexpression of the cyclin D1 and PERK (protein kinase R-like endoplasmic reticulum kinase) in ER-positive breast cancer cell lines [45].

5.2. Combined active derivative therapy

Curcumin is the active ingredient extracted from turmeric and has a wide range of pharmacological effects, including anti-tumor, anti-bacterial, anti-inflammatory, anti-oxidant, anti-hepatotoxic, anti-hyperlipidemic, anti-viral and anti-Alzheimer's disease effects [46].Curcumin and emodin are both potent anticancer agents, and GUO et al. found that curcumin and emodin synergistically inhibited the proliferation and invasion of breast cancer cells through the up-regulation of miR-34a, the combination of the two reduced breast cancer cell viability and induced apoptosis, and that the combination also synergistically inhibited invasion. Thus, the combination of the two compounds suggests new directions for clinical practice and modern medicine in applying breast cancer therapy [47].In addition, the combination therapy of emodin with berberine is promising. Berberine is an isoquinoline alkaloid isolated from Berberis vulgaris. It has a wide range of pharmacological properties, inhibiting the proliferation of various cancer cells and hindering invasion and metastasis. Recent evidence suggests that berberine may improve the efficacy and safety of radiotherapy [48]. Lavanya Ponnusamyet et al.found that emodin and berberine exert anticancer effects by inhibiting the SIK3/mTOR/Akt pathway, thereby inhibiting breast cancer growth and promoting apoptosis. However, further studies in vivo and in other clinical cancer models are needed for clinical therapeutic applications [49].Finally, Yan et al. demonstrated that the combination of emodin-8-O-β-D glucoside (EG) and paclitaxel (PTX) synergistically inhibit the viability and invasive metastasis of human breast cancer cells in vitro based on the cellular level, but the clinical studies are still needed to explore whether the combination of the two drugs can exert the effect of inhibition of tumor growth and metastasis in vivo [50].However, further studies in vivo and in other clinical cancer models are needed for clinical therapeutic applications [49].

6. Concluding remarks and outlook for the future

In recent years, TCM can regulate the balance of the body from the holistic view of the organism, reduce drug resistance in tumors, improve the quality of life of patients, and achieve the purpose of treating diseases [51]. Many chemical components contained in TCM have been extracted and widely used in clinical practice, and have shown better efficacy. Emodin is a natural anthraquinone active ingredient extracted from the plant rhubarb, and a large number of studies have shown that it has great potential in tumor therapy, especially in breast cancer treatment. Emodin can inhibit many types of breast cancer by acting on different targets, and it is expected to become a broad-spectrum new anticancer drug in the future.

However, the poor solubility and low oral utilization of emodin have affected its application in clinical practice. Therefore, designing novel emodin derivatives or utilizing novel drug delivery systems to improve drug utilization or efficacy will be one of the future research directions. In addition, with a deeper understanding of the mechanism of action, the combined use of different drug groupings to improve the efficacy is also one of the future research directions.

The toxic effects of emodin have been of concern to researchers for a long time. The toxic effects on the liver have been extensively reported, and in vitro studies have shown that 30uM of emodin can induce time-dependent apoptosis of L-02 cells [52].In addition, emodin may interfere with the metabolism of glutathione (GSH) and fatty acids in human liver [53].There are also studies showing that the hepatotoxicity of emodin may be induced by activating the IRE1 α - XBP1 axis to induce endoplasmic reticulum stress in HepG2 cells, thereby inducing hepatocyte apoptosis [54].Animal experiments also showed that after intervention with 30 mg/kg and 90 mg/kg emodin, although no abnormalities were found in rat liver function tests, morphological observations showed a significant increase in hepatic inflammatory cell infiltration and slight changes in hepatic sinus structure [55].

At the same time, studies have shown that emodin also has nephrotoxicity. After intraperitoneal injection of emodin (0.4, 0.6, and 0.8 g/kg) for 14 days, mouse renal tubular epithelial cells were significantly damaged, endothelial cells were swollen, blood clots were formed in the blood vessels, and blood urea nitrogen and creatinine levels were significantly increased. The mechanism is related to the iron induced apoptosis induced by emodin by inhibiting the Notch1/Nrf2/glutathione peroxidase 4-axis [56].

Also, emodin also has reproductive toxicity, which can significantly reduce sperm count and inhibit its activity. Especially at extremely high concentrations (4 g/kg), it can cause irreversible damage [57].

Although emodin has hepatorenal and reproductive toxicity, with the invention of new dosage forms and delivery systems, its toxicity and side effects can be significantly reduced while increasing its solubility and oral utilization [55].

The use of emodin in clinical medicine is still relatively immature, but human beings are working on various ways to find effective methods and drugs to treat cancer in order to achieve the goal of curing cancer.

Due to its wide range of pharmacological effects and high efficacy as an anticancer active ingredient, emodin has always been a hotspot in the research of domestic and foreign pharmaceutical scholars.

In summary, emodin can inhibit breast cancer cell proliferation, induce tumor cells, anti-metastasis and play an important role in breast cancer treatment in various ways.

CRediT authorship contribution statement

Ruoqing Chen: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Hairong Zhang:** Resources, Project administration, Methodology. **Xue Zhao:** Validation, Supervision, Software. **Lin Zhu:** Investigation, Funding acquisition. **XiaoYu Zhang:** Data curation, Conceptualization. **Yuning Ma:** Visualization, Validation, Supervision. **Lei Xia:** Validation, Resources, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

References

[1] C. Núñez, Blood-based protein biomarkers in breast cancer[J/OL], Clin. Chim. Acta 490 (2019) 113–127, https://doi.org/10.1016/j.cca.2018.12.028.
[2] K. Asleh, N. Riaz, T.O. Nielsen, Heterogeneity of triple negative breast cancer: current advances in subtyping and treatment implications[J/OL], J. Exp. Clin. Cancer Res. 41 (1) (2022) 265, https://doi.org/10.1186/s13046-022-02476-1.
[3] E.A. Rakha, F.G. Pareja, New advances in molecular breast cancer pathology[J/OL], Semin. Cancer Biol. 72 (2021) 102–113, https://doi.org/10.1016/j.semcancer.2020.03.014.
[4] E Orrantia-Borunda, P Anchondo-Nuñez, LE Acuña-Aguilar, FO Gómez-Valles, CA Ramírez-Valdespino, Tectônica de sal nas bacias de Cumuruxatiba, de Almada e de Camamu, in: HN Mayrovitz (Ed.), Breast Cancer [Internet], Exon Publications, Brisbane (AU), 2022 Aug 6. Chapter 3. PMID: 36122153.
[5] EA Perez, EH Romond, VJ Suman, JH Jeong, G Sledge, Jr Geyer CE, S Martino, P Rastogi, J Gralow, SM Swain, EP Winer, G Colon-Otero, NE Davidson, E Mamounas, JA Zujewski, N Wolmark, Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831, J Clin Oncol. 32 (33) (2014 Nov 20) 3744–3752, https://doi.org/10.1200/JCO.2014.55.5730. Epub 2014 Oct 20. PMID: 25332249; PMCID: PMC4226805.
[6] O. Pagani, M.M. Regan, B.A. Walley, et al., Adjuvant exemestane with ovarian suppression in premenopausal breast cancer[J/OL], N. Engl. J. Med. 371 (2) (2014) 107–118, https://doi.org/10.1056/NEJMoa1404037.
[7] Li Yunxiang, Yinku Liang, Feixiong Gao, et al., Research progress of traditional Chinese medicine in treating breast cancer[J/OL], Chin. J. Exp. Tradit. Med. Formulae 25 (3) (2019) 211–219, https://doi.org/10.13422/j.cnki.syfjx.20182328.
[8] M. C, W. B, Z. Q, et al., Emodin induces apoptosis and autophagy of fibroblasts obtained from patient with ankylosing spondylitis[J/OL], Drug Des. Dev. Ther. 13 (2019), https://doi.org/10.2147/DDDT.S182087 [2023-10-18], https://pubmed.ncbi.nlm.nih.gov/30809091/.
[9] N. Ketelut-Carneiro, K.A. Fitzgerald, Apoptosis, pyroptosis, and necroptosis—oh my! The many ways a cell can die[J/OL], J. Mol. Biol. 434 (4) (2022) 167378, https://doi.org/10.1016/j.jmb.2021.167378.
[10] X. Xu, Y. Lai, Z.C. Hua, Apoptosis and apoptotic body: disease message and therapeutic target potentials[J/OL], Biosci. Rep. 39 (1) (2019) BSR20180992, https://doi.org/10.1042/BSR20180992.
[11] W.Y. Li, R.Y.K. Chan, P.H.F. Yu, et al., Emodin induces cytotoxic effect in human breast carcinoma MCF-7 cell through modulating the expression of apoptosis-related genes[J/OL], Pharmaceut. Biol. 51 (9) (2013) 1175–1181, https://doi.org/10.3109/13880209.2013.782322.
[12] N. Zhang, J. Wang, A. Sheng, et al., Emodin inhibits the proliferation of MCF-7 human breast cancer cells through activation of aryl hydrocarbon receptor (AhR) [J/OL], Front. Pharmacol. 11 (2021) 622046, https://doi.org/10.3389/fphar.2020.622046.
[13] C. Zu, M. Zhang, H. Xue, et al., Emodin induces apoptosis of human breast cancer cells by modulating the expression of apoptosis-related genes[J/OL], Oncol. Lett. 10 (5) (2015) 2919–2924, https://doi.org/10.3892/ol.2015.3646.
[14] Z. Huang, G. Chen, P. Shi, Emodin-induced apoptosis in human breast cancer BCap-37 cells through the mitochondrial signaling pathway[J/OL], Arch Pharm. Res. (Seoul) 31 (6) (2008) 742–748, https://doi.org/10.1007/s12272-001-1221-6.
[15] Fu Qiao, Wei Zhang, Jun Yang, et al., Expression of lncRNAPCGEM1 in prostate cancer tissues and its effect on the proliferation,apoptosis,invasion,migration and epithelial mesenchymal transition of prostate cancer PC3 cells.[J/OL], J. Clin. Urol. 38 (11) (2023) 856–861+866, https://doi.org/10.13201/j.issn.1001-1420.2023.11.010.
[16] M. Cardano, C. Tribioli, E. Prosperi, Targeting proliferating cell nuclear antigen (PCNA) as an effective strategy to inhibit tumor cell proliferation[J/OL], Curr. Cancer Drug Targets 20 (4) (2020) 240–252, https://doi.org/10.2174/1568009620666200115162814.
[17] X. Song, X. Zhou, Y. Qin, et al., Emodin inhibits epithelial-mesenchymal transition and metastasis of triple negative breast cancer via antagonism of CC-chemokine ligandï¿½5 secreted from adipocytes[J/OL], Int. J. Mol. Med. (2018), https://doi.org/10.3892/ijmm.2018.3638 [2023-11-11], http://www.spandidos-publications.com/10.3892/ijmm.2018.3638.
[18] J.Q. Sui, K.P. Xie, W. Zou, et al., Emodin inhibits breast cancer cell proliferation through the erα-MAPK/akt-cyclin D1/bcl-2 signaling pathway[J/OL], Asian Pac. J. Cancer Prev. APJCP 15 (15) (2014) 6247–6251, https://doi.org/10.7314/APJCP.2014.15.15.6247.
[19] E. Sakalli-Tecim, P. Uyar-Arpaci, N.T. Guray, Identification of potential therapeutic genes and pathways in phytoestrogen emodin treated breast cancer cell lines via network biology approaches[J/OL], Nutr. Cancer 74 (2) (2022) 592–604, https://doi.org/10.1080/01635581.2021.1889622.
[20] L. Zhang, Y.K. Lau, L. XI, et al., Tyrosine kinase inhibitors, emodin and its derivative repress HER-2/neu-induced cellular transformation and metastasis-associated properties[J/OL], Oncogene 16 (22) (1998) 2855–2863, https://doi.org/10.1038/sj.onc.1201813.
[21] H. Jayasuriya, N.M. Koonchanok, R.L. Geahlen, et al., Emodin, a protein tyrosine kinase inhibitor from Polygonum cuspidatum[J/OL], Journal of Natural Products 55 (5) (1992) 696–698, https://doi.org/10.1021/np50083a026.
[22] L Zhang, YK Lau, W Xia, GN Hortobagyi, MC Hung, Tyrosine kinase inhibitor emodin suppresses growth of HER-2/neu-overexpressing breast cancer cells in athymic mice and sensitizes these cells to the inhibitory effect of paclitaxel, Clin Cancer Res. 5 (2) (1999 Feb) 343–353. PMID: 10037184.
[23] S. Iwanowycz, J. Wang, J. Hodge, et al., Emodin inhibits breast cancer growth by blocking the tumor-promoting feedforward loop between cancer cells and macrophages[J/OL], Mol. Cancer Therapeut. 15 (8) (2016) 1931–1942, https://doi.org/10.1158/1535-7163.MCT-15-0987.
[24] Y. Suhail, M.P. Cain, K. Vanaja, et al., Systems biology of cancer metastasis[J/OL], Cell Systems 9 (2) (2019) 109–127, https://doi.org/10.1016/j.cels.2019.07.003.
[25] X. Zhang, L. Zhu, X. Wang, et al., Basic research on curcumin in cervical cancer: progress and perspectives[J/OL], Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 162 (2023) 114590, https://doi.org/10.1016/j.biopha.2023.114590.
[26] A.A. Abdellatef, M. Fathy, A.E.S.I. Mohammed, et al., Inhibition of cell-intrinsic NF-κB activity and metastatic abilities of breast cancer by aloe-emodin and emodic-acid isolated from Asphodelus microcarpus[J/OL], J. Nat. Med. 75 (4) (2021) 840–853, https://doi.org/10.1007/s11418-021-01526-w.
[27] B. Jelassi, M. Anchelin, J. Chamouton, et al., Anthraquinone emodin inhibits human cancer cell invasiveness by antagonizing P2X7 receptors, Carcinogenesis 34 (7) (2013) 1487–1496, https://doi.org/10.1093/carcin/bgt099.
[28] A.T. Sougiannis, B. Vanderveen, I. Chatzistamou, et al., Emodin reduces tumor burden by diminishing M2-like macrophages in colorectal cancer[J/OL], Am. J. Physiol. Gastrointest. Liver Physiol. 322 (3) (2022) G383–G395, https://doi.org/10.1152/ajpgi.00303.2021.
[29] S.J. Mcdonald, B.M. Bullard, B.N. Vanderveen, et al., Emodin reduces surgical wounding-accelerated tumor growth and metastasis via macrophage suppression in a murine triple-negative breast cancer model[J/OL], Physiological Reports 11 (19) (2023) e15813, https://doi.org/10.14814/phy2.15813.

[30] Q. Liu, J. Hodge, J. Wang, et al., Emodin reduces Breast Cancer Lung Metastasis by suppressing Macrophage-induced Breast Cancer Cell Epithelial-mesenchymal transition and Cancer Stem Cell formation[J/OL], Theranostics 10 (18) (2020) 8365–8381, https://doi.org/10.7150/thno.45395.
[31] S. Yu, J. Zheng, Y. Zhang, D. Meng, Y. Wang, X. Xu, N. Liang, S. Shabiti, X. Zhang, Z. Wang, Z. Yang, P. Mi, X. Zheng, W. Li, H. Chen, The mechanisms of multidrug resistance of breast cancer and research progress on related reversal agents, Bioorg. Med. Chem. 95 (2023 Nov 15) 117486, https://doi.org/10.1016/j.bmc.2023.117486. Epub 2023 Sep 30. PMID: 37847948.
[32] K.H. Yu, I.T. Wu, C.P. Yu, W.C. Wang, C.H. Chi, K.C. Tsai, C.H. Chou, C.C. Hung, H.Y. Hung, Discovery of oral chemotherapeutic reversal agents for treating multidrug resistance cancer, Eur. J. Pharmacol. 977 (2024 May 31) 176682, https://doi.org/10.1016/j.ejphar.2024.176682. Epub ahead of print. PMID: 38823759.
[33] J min Fu, J. Zhou, J. Shi, et al., Emodin affects ERCC1 expression in breast cancer cells[J/OL], J. Transl. Med. 10 (S1) (2012) S7, https://doi.org/10.1186/1479-5876-10-S1-S7.
[34] J. Kim, M.K. Shim, S. Yang, et al., Combination of cancer-specific prodrug nanoparticle with Bcl-2 inhibitor to overcome acquired drug resistance[J/OL], J. Contr. Release 330 (2021) 920–932, https://doi.org/10.1016/j.jconrel.2020.10.065.
[35] I. Buondonno, E. Gazzano, E. Tavanti, et al., Endoplasmic reticulum-targeting doxorubicin: a new tool effective against doxorubicin-resistant osteosarcoma[J/OL], Cell. Mol. Life Sci. 76 (3) (2019) 609–625, https://doi.org/10.1007/s00018-018-2967-9.
[36] B. Li, X. Zhao, L. Zhang, et al., Corrigendum: Emodin Interferes With AKT1-Mediated DNA Damage and Decreases Resistance of Breast Cancer Cells to Doxorubicin[J/OL], Front. Oncol. 11 (2021) 687841, https://doi.org/10.3389/fonc.2021.687841.
[37] Y. Jia, Z. Sheng, D. Hu, et al., Highly penetrative liposome nanomedicine generated by a biomimetic strategy for enhanced cancer chemotherapy[J/OL], Biomater. Sci. 6 (6) (2018) 1546–1555, https://doi.org/10.1039/C8BM00256H.
[38] D.E. Large, R.G. Abdelmessih, E.A. Fink, et al., Liposome composition in drug delivery design, synthesis, characterization, and clinical application[J/OL], Adv. Drug Deliv. Rev. 176 (2021) 113851, https://doi.org/10.1016/j.addr.2021.113851.
[39] Y. Song, Z. Sheng, Y. Xu, et al., Magnetic liposomal emodin composite with enhanced killing efficiency against breast cancer[J/OL], Biomater. Sci. 7 (3) (2019) 867–875, https://doi.org/10.1039/c8bm01530a.
[40] M. Bhattacharjee, P. Upadhyay, S. Sarker, et al., Combinatorial therapy of Thymoquinone and Emodin synergistically enhances apoptosis, attenuates cell migration and reduces stemness efficiently in breast cancer[J/OL], Biochim. Biophys. Acta Gen. Subj. 1864 (11) (2020) 129695, https://doi.org/10.1016/j.bbagen.2020.129695.
[41] F.A. Fisusi, E.O. Akala, Drug Combinations in Breast Cancer Therapy[J/OL], Pharm. Nanotechnol. 7 (1) (2019) 3–23, https://doi.org/10.2174/2211738507666190122111224.
[42] C. Zu, G. Qin, C. Yang, et al., Low dose Emodin induces tumor senescence for boosting breast cancer chemotherapy via silencing NRARP[J/OL], Biochem. Biophys. Res. Commun. 505 (4) (2018) 973–978, https://doi.org/10.1016/j.bbrc.2018.09.045.
[43] S. Malik, A. Singh, P. Negi, et al., Thymoquinone: A small molecule from nature with high therapeutic potential[J/OL], Drug Discov. Today 26 (11) (2021) 2716–2725, https://doi.org/10.1016/j.drudis.2021.07.013.
[44] Ahmad I Shagufta, Tamoxifen a pioneering drug: An update on the therapeutic potential of tamoxifen derivatives, Eur. J. Med. Chem. 143 (2018 Jan 1) 515–531, https://doi.org/10.1016/j.ejmech.2017.11.056. Epub 2017 Nov 24. PMID: 29207335.
[45] Y.G. Kim, Y.H. Park, E.Y. Yang, et al., Inhibition of tamoxifen's therapeutic effects by emodin in estrogen receptor-positive breast cancer cell lines[J/OL], Annals of Surgical Treatment and Research 97 (5) (2019) 230, https://doi.org/10.4174/astr.2019.97.5.230.
[46] SA Noureddin, RM El-Shishtawy, KO Al-Footy, Curcumin analogues and their hybrid molecules as multifunctional drugs, Eur. J. Med. Chem. 182 (2019 Nov 15) 111631, https://doi.org/10.1016/j.ejmech.2019.111631. Epub 2019 Aug 19. PMID: 31479974.
[47] J. Guo, W. Li, H. Shi, et al., Synergistic effects of curcumin with emodin against the proliferation and invasion of breast cancer cells through upregulation of miR-34a[J/OL], Mol. Cell. Biochem. 382 (1–2) (2013) 103–111, https://doi.org/10.1007/s11010-013-1723-6.
[48] D. Song, J. Hao, D. Fan, Biological properties and clinical applications of berberine[J/OL], Front. Med. 14 (5) (2020) 564–582, https://doi.org/10.1007/s11684-019-0724-6.
[49] L. Ponnusamy, G. Kothandan, R. Manoharan, Berberine and Emodin abrogates breast cancer growth and facilitates apoptosis through inactivation of SIK3-induced mTOR and Akt signaling pathway[J/OL], Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1866 (11) (2020) 165897, https://doi.org/10.1016/j.bbadis.2020.165897.
[50] Yan Yishu, Zhao Yan, Tiangong Lu, et al., Emodin -8-O-β-D-glucoside combined with paclitaxel inhibits the viability and metastasis of human breast cancer cells [J/OL], Chinese Journal of Pharmacovigilance 20 (7) (2023) 728–734, https://doi.org/10.19803/j.1672-8629.20230243.
[51] Q. Wu, H. Yan, Z. Kang, A Review of Traditional Chinese Medicine for Triple Negative Breast Cancer and the Pharmacological Mechanisms, Am. J. Chin. Med. 14 (2024 Jun) 1–25, https://doi.org/10.1142/S0192415X2450040X. Epub ahead of print. PMID: 38879747.
[52] C.L. Li, J. Ma, L. Zheng, H.J. Li, P. Li, Determination of emodin in L-02 cells and cell culture media with liquid chromatography-mass spectrometry: application to a cellular toxicokinetic study, J. Pharm. Biomed. Anal. 71 (2012 Dec) 71–78, https://doi.org/10.1016/j.jpba.2012.07.031. Epub 2012 Aug 19. PMID: 22944356.
[53] X. Liu, Y. Liu, M. Cheng, H. Xiao, Metabolomic Responses of Human Hepatocytes to Emodin, Aristolochic Acid, and Triptolide: Chemicals Purified from Traditional Chinese Medicines, J. Biochem. Mol. Toxicol. 29 (11) (2015 Nov) 533–543, https://doi.org/10.1002/jbt.21724. Epub 2015 Jul 7. PMID: 26149242.
[54] S.B. Park, G.H. Cho, Y.E. Park, H.S. Chun, Emodin, an Emerging Mycotoxin, Induces Endoplasmic Reticulum Stress-Related Hepatotoxicity through IRE1α-XBP1 Axis in HepG2 Cells, Toxins 15 (7) (2023 Jul 12) 455, https://doi.org/10.3390/toxins15070455. PMID: 37505724; PMCID: PMC10467057.
[55] Y. Yao, F. Shao, X. Peng, H. Wang, K. Wang, K. Zhu, Emodin in-situ delivery with Pluronic F-127 hydrogel for myocardial infarction treatment: Enhancing efficacy and reducing hepatotoxicity, Life Sci. 354 (2024 Aug 8) 122963, https://doi.org/10.1016/j.lfs.2024.122963. Epub ahead of print. PMID: 39127316.
[56] M. Xing, X. Ma, X. Wang, H. Wang, M. Xie, Z. Zhang, J. Zhou, Emodin disrupts the Notch1/Nrf2/GPX4 antioxidant system and promotes renal cell ferroptosis, J. Appl. Toxicol. 43 (11) (2023 Nov) 1702–1718, https://doi.org/10.1002/jat.4509. Epub 2023 Jul 2. PMID: 37393915.
[57] T. Luo, N. Li, Y.Q. He, S.Q. Weng, T. Wang, Q.X. Zou, X.H. Zeng, Emodin inhibits human sperm functions by reducing sperm [Ca(2+)]i and tyrosine phosphorylation, Reprod. Toxicol. 51 (2015 Jan) 14–21, https://doi.org/10.1016/j.reprotox.2014.11.007. Epub 2014 Nov 22. PMID: 25463531.