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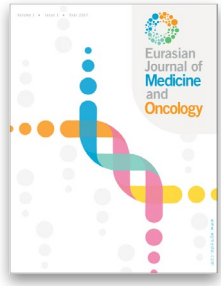

Review

The Real Mechanisms of Emodin Treating Lung Cancer Based on System Pharmacology

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Abstract

In the world nowadays, cancer gradually becomes the first problem to public health and seriously threatens human life due to the high mortality and recurrence. In modern medical theory, cancer is considered as a genetic disease presenting either oncogene activation (OCG) or tumor suppressor gene (TSG) inactivation. Many clinical observations showed that the existing standard chemotherapies which target oncogenes and their related molecules have little benefit in improving survival, prognosis, recurrence and metastasis despite tumor size shrinkage. Compared with these routine treatment methods, the traditional Chinese medicine (TCM) cancer therapy based on TCM theory, in which the cancer initiation is regarded as disorder of human body system, focuses on the events impacting the gene rather than the gene itself. In fact, it is necessary but not sufficient for cancer initiation and progression to activate OCG or inactivate TSG, which exhibit oncogene or tumor-suppressor property depending on the biological context. In TCM theory, lung and large intestine are external-internal relations of each other, which are physiologically related and pathologically affected each other. Hence, the use of a classical laxative medicine rhubarb for lung cancer treatment is in line with TCM theory. Emodin as the major component of rhubarb represents the multi-targeting therapeutic mechanisms of TCM in multiple disease treatment including anti-cancer. There are some reviews on microscopic and inner mechanisms of emodin in cancer treatment, our previous study confirmed lung cancer-preventing effect of lung cancer. Here, we summarize the real mechanisms of emodin treating lung cancer based on system pharmacology, mainly focusing on the resolution of intrinsic pathological inducers, which will provide a solid foundation to understand cancer pathogenesis and formulate cancer therapy.

Keywords: Emodin, Lung cancer, Traditional Chinese medicine (TCM) theory

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In the world nowadays, cancer gradually becomes the first problem to public health, whereas lung cancer accounts for the largest proportion of cancer-related deaths.[1] The conventional treatments on lung cancer include surgery, radiotherapy and chemotherapy.[2] However, most patients lost the chance of operation because they are diagnosed too late, and chemotherapy and radiation become the most common clinical treatment strategies for lung cancer.[3, 4] A lot of clinical observations showed that the existing standard chemotherapies have little benefit in improving survival, prognosis, recurrence and metastasis because of severe adverse reactions, such as gastrointestinal reactions, fatigue and anemia, cardiotoxicity, bone-marrow suppression, liver and kidney injury and so on,[5] which reduced greatly the life quality.

In modern medical theory, cancer is considered as a genetic disease presenting either oncogene activation (OCG) or tumor-suppressor gene (TSG) inactivation.[6] In fact, it is necessary but not

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sufficient for cancer initiation and progression to activate OCG or inactivate TSG, which exhibit oncogene or tumor suppressor property depending on the biological context, for example, the hepatocarcinoma cells could translate to normal phenotypes after injected into the liver parenchyma of a healthy rats.[7] Therefore, cancer therapy should focus on the event impacting the gene rather than the gene itself. Traditional Chinese medicine (TCM) has been effectively utilized as a primary treatment in China for more than 2000 years and play an indispensable role in the whole course of cancer prevention and therapy,[8] thereby forming a unique and complete theory. Based on the TCM theory, cancer initiation is induced by the cancerous conditions, namely unbalance between exogenous pathogenic factors and endogenous physical conditions, in which the pathogenic factors excel over the body's own defense.[9] Based on the TCM theory, TCM possesses advantages over Western medicine in cancer treatment, such as improving symptoms and life quality,[10] preventing tumorigenesis, reducing tumor recurrence and metastasis, and so on.[11, 12] Conventional *chemotherapeutics usually* focus on only one single target, TCM, however, *could modulate multiple targets to treat diseases*.[13, 14] In other words, unlike conventional *chemotherapeutics* which focus on the tumor mass, the focus of TCM for cancer therapy is on the patient.[15]

Emodin (1,3,8-trihydroxy-6methylanthraquinone) as the major component of a traditional medicine rhubarb (also named Rhei or Dahuang), represents the multi-targeting therapeutic mechanisms of TCM in multiple disease treatment including anti-cancer.[16] There are some reviews on microscopic and inner mechanisms of emodin in cancer treatment, including triggering endoplasmic reticulum stress and cell autophagy,[17, 18] suppressing PI3K/AKT signal *transduction and* methyltransferase expression,[19] promoting p53 tumor-suppressive functions and p38 phosphorylation,[20] inhibiting CK2 activation and ERK phosphorylation,[21, 22] promoting specific protein cyclophilin D of mitochondrial matrix expression and so on,[23] by which emodin exerts anti-tumor effect against most cancer cell lines.[24, 25] However, it is confusing that emodin used to directly treat cells is more than 10 μM in all in vitro studies (over 10 times of maximum concentration), but its oral and intravenous bioavailability is unsatisfactory (maximum blood concentration, 0.20 μM), which makes these studies lost the convincing and disconnect from clinical practice. In addition, emodin in vitro from 10 to 50 μM displayed potent cytotoxicity on cancer cells and nearly no cytotoxicity on normal cells, whereas the same dose of emodin also showed efficacy against tissue inflammation, tissue injury, diabetes, microbial infection, fibrosis, and so on.[26] Obviously, these studies do not explain *how emodin* fulfill anti-cancer potential, and *there is no* published paper to unite the real mechanism of emodin treating cancer. However, the understanding of these mechanisms is rewarding, which could help us enhance the efficacy of TCM on cancer treatment in a logical and rational way. Hence, we summarize how emodin prevent lung cancer based on system pharmacology, mainly focusing on the resolution of intrinsic pathological inducers, which will provide a solid foundation to understand cancer pathogenesis and formulate cancer therapy.

1. Emodin Promotes Lung Injury Healing

It is well known that the injury and cancerization are linked based on epidemiology. Cancer is usually regarded as an incurable wound that due to the many histological and molecular similarities between the wound healing and tumour formation.[27] Wound repair needs the static epithelial cells to develop a phenotype of epithelial-to-mesenchymal transition (EMT), which creates a microenvironment to promote cancer initiation,[28, 29] whereas cancer reflects the abnormal physiological reaction to injury characterized by a state of chronic inflammation which facilitates the tumorigenesis process or reawakens dormant tumor cells.[30] There are many cases reflecting chronic wounds as well-known risk factors for tumour initiation, for example, Crohn's disease and ulcerative colitis could increase the risk of colon cancer,[31, 32] ulcerative gastritis has an increased risk of developing inflammation-driven gastric cancer,[33, 34] the malignant transformation of Marjolin´s ulcer as a carcinomatous degeneration is unquestionable among the dermatological field, and so on.[35, 36] The wound healing response to a chronic injury requires inflammation trigger and extracellular matrix remodeling which is also a central event to the tumorigenesis cascade.[37] The lung epithelial cells can be regenerated by stem-like sub-populations upon injury due to facultative regeneration capability, which allows the relatively quiescent tissue to apace respond to continual injury induced by a common trigger.[38] We proposed "no wound no cancer" and that wound healing may prevent cancer initiation by reducing proinflammatory factors and eliminating the cell debris. We found that urethane-induced lung carcinogenesis was related with injury independent of pulmonary inflammation and that the wound healing-like microenvironment may facilitate tumor.[39] Moreover, we also found that momordicoside G could facilitate wound healing against lung cancer, simultaneously, macrophages play a very important role in the lung injury repair and carcinoma lesion.[40]

It is recognized that inflammation is a key characteristic of carcinogens,[41] which initiate DNA damage, tissue injury and tumour initiation.[42] It was reported that emodin could inhibit the NLRP3 inflammasome mediated neutrophil recruitment and pyroptosis signaling pathway to ameliorate the lung injury induced by acute pancreatitis or LPS.[43, 44] In the pathological injury of intestinal/lung tissues, emodin suppressed proinflammatory cytokines and NF-κB nuclear accumulation, inhibited ASC, caspase-1, NLRP3 and HO-1 expressions, promoted Nrf2 nuclear translocation.[45] In sepsis-induced pulmonary pathological changes, emodin could upregulate AQP and TJ expression, remarkably reduced the inflammatory factor secretion and pulmonary apoptosis, therefore repairing lung epithelial barrier and reducing death rate.[46] In bleomycin-caused lung injury, emodin markedly alleviated collagen overproduction, lung structural distortion, inflammatory cells infiltration and inflammatory factor secretion, while stimulating the Nrf2-antioxidant signaling and preventing EMT.[47] Furthermore, emodin could inhibit neutrophil proteases activity to protect lung from injury.[48] Moik et al. reported that emodin could suppress the Notch

and NF-κB signals and promote TUG1 expression to relieve LPS-induced inflammation.[49] Han et al. reported that emodin can reduce caspase-1 secretion and cleaved IL-1β attenuation by inhibiting activation of NLRP3 inflammasome.[50] Xu et al. reported that emodin could observably mitigate formation of SAP-upregulated cold-inducible RNA-binding protein and NLRP3 inflammasome to inhibit pulmonary neutrophil infiltration.[51] Furthermore, some studies revealed that emodin could significantly upregulate miRNA-30a expression to mitigate sodium taurocholate-induced inflammatory injury,[52] reverse LPS-induced decreased miR-21 expression and thereby inhibited PTEN and blunted NF-κB signaling.[53]

To further illustrate the potential mechanism associated with injury healing effect of emodin, a relevant network pharmacology was conducted (Fig. 1). There are 46 potential targets associated with injury healing effect of emodin, the protein-protein interaction network was showed in Figure 1a. The KEGG enrichment analysis revealed that these targets were significantly involved in 49 wound injury related pathways ($p \leq 0.05$), as mentioned above, among which "microRNAs in cancer" and "apoptosis", "NF-kappa B signaling pathway", "non-small cell lung cancer" and "inflammatory bowel disease" signaling pathways are reported to be regulated by emodin. And the GO analysis revealed that these targets are participate in 90 injury healing related biological processes ($p \leq 0.01$), among which "inflammatory response", "organ regeneration", "cell proliferation" and so on biological processes are related to injury healing, but there is still unknown clue to explore. For example, there are reported that emodin could regulate "MAPK signaling pathway" and "PI3K-Akt signaling pathway" to inhibit breast cancer progress,[54] but these effects of emodin on lung cancer is still unclear.

2. Emodin Prevents System Hypercoagulable State

Venous thromboembolism (VTE) is common in cancer patients,[55] in Danish medical registries, the comparison between 499,092 cancer patients and 1,497,276 general populations between 1997 and 2017 showed a 9-fold higher risk of VTE in cancer patients than in the normal persons.[56] The recent information from the National Cancer Center indicated that one of the most common complications of lung cancer is VTE.[57] The factors associated with this risk include platelet activation,[58] impaired fibrinolysis, immune checkpoint inhibitor therapy,[49] blood infusion and so on.[59] Typically, VTE mainly involves the endothelial cell injury and blood hypercoagulable state.[60] Generally speaking, thrombosis formation is induced by intrinsic and extrinsic coagulation systems,[61] platelet activation and polymerization are essential events in the thrombus formation, and thrombin has a vital role in cascade blood coagulation.[62]

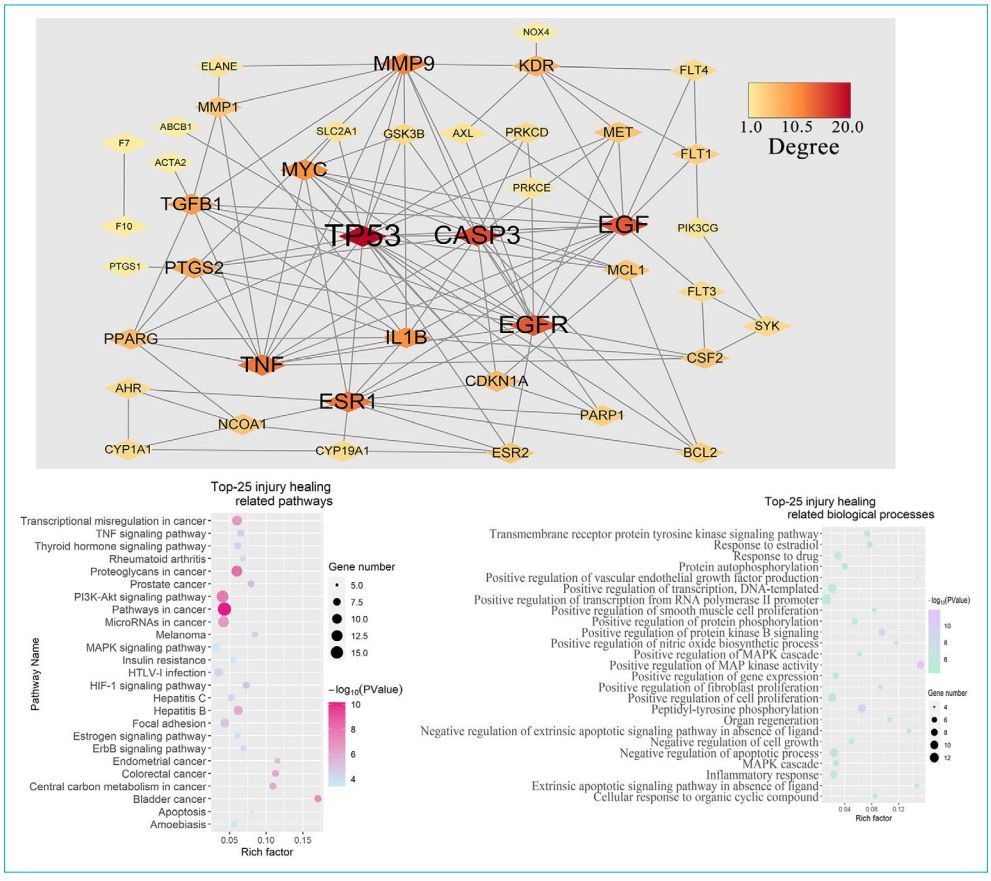

Figure 1. Potential mechanism associated with injury healing effect of emodin; **(a)** Protein-protein interaction network of 46 potential targets associated with injury healing effect of emodin; **(b)** The potential targets involved in KEGG pathways; **(c)** The potential targets involved in biological processes.

Currently, the traditional VTE therapies included *thrombolytic*, anti-coagulation and antiplatelet drugs have some limitations due to higher risk of haemorrhage, unpredictable efficacy and great interactions between drugs.[63] Though the association between VTE and lung cancer is very clear, the underlying mechanisms are still *ambiguous*.[61, 64] The existing assessment criteria of VTE risk, such as the Khorana score, the PROTECHT score and the CONKO score, fail to identify many high-risk individuals, which is a challenge for ambulatory patients to prevent thrombus formation.[65] It is believed that malignancy itself may induce a thrombophilia and hypercoagulable state by increasing venous stasis, endothelial injury and pro-thrombotic factors.[66] The occurrence of these symptoms may be the basis of cancer-related VTE.[67] Previous study showed that it was ALK rearrangements but not EGFR or KRAS mutations to increase the risk of VTE in lung cancer patients.[68] Correspondingly, VTE itself influences tumor development and prognosis beyond interfering with the clotting system.[69] TCM has unique advantages in VTE treatment with long effect duration and high compliance as well as less side effects and low toxicity.[70]

Rhubarb, one of the most frequently-used herbs in TCM, could improve the blood circulation, slower blood coagulation and relieve stasis in clinic.[71] Emodin, a major bioactive ingredient of rhubarb, has a variety of pharmacological effects. In previous studies, emodin could target multiple symptoms of cardiovascular diseases through multiple pathways.[72, 73] Wu et al found that emodin could significantly improve aorta vasorelaxation and promote NO production.[37] According to modern pathology, local blood vessel inflammation and can induce the thrombus formation.[74] Nemmar et al found that emodin has consistently protective effect to against DEP-induced injury of vascular and cardiac homeostasis,[75] which agreed with promoting blood circulation of rhubarb in TCM theory. We proposed hypercoagulation also involved in lung carcinogenesis and found that there were the gradual hypercoagulation during urethane-induced lung carcinogenic model and the cancer-prevention effect of emodin was related to its anti-thrombosis effect.[76]

To further illustrate the potential mechanism of emodin in prevention of system hypercoagulable state, a relevant network pharmacology was conducted (Fig. 2). Emodin has 18 potential targets associated with hypercoagulable state prevention, the protein-protein interaction network was showed in Figure 2a. The KEGG enrichment analysis revealed that these targets were significantly enriched in 23 hypercoagulable state related pathways ($p \leq 0.05$), among which "FoxO signaling pathway" and "PI3K-Akt signaling pathway" are relate to thrombogenesis,[77, 78] however, there are no experimental reports about emodin acting on these two pathways. And the GO analysis revealed that these targets are participate in 48 hypercoagulable state related biological process ($p \leq 0.01$), among which "blood coagulation, extrinsic pathway" is relate to thrombogenesis, "positive regulation of NF-kappaB transcription factor activity" has correlation with the pharmacological effect of emodin.[79]

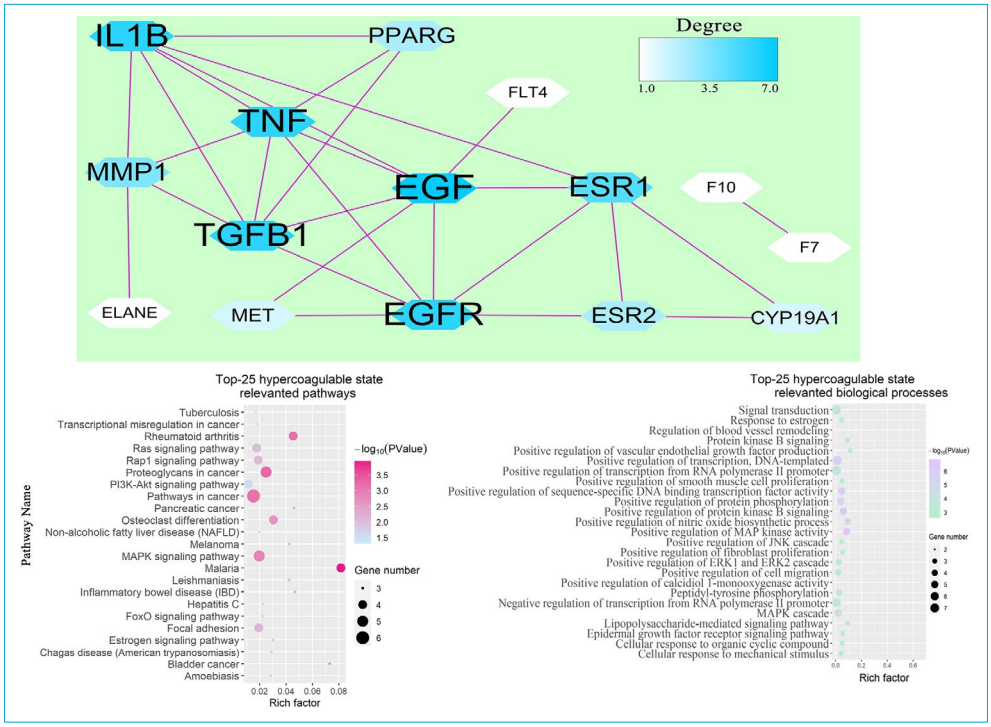

Figure 2. Potential mechanism associated with coagulation preventing effect of emodin; **(a)** Protein-protein interaction network of potential targets associated with coagulation preventing effect of emodin; **(b)** The potential targets involved in KEGG pathways; **(c)** The potential targets involved in biological processes.

3. Emodin Promotes the Elimination of Poisonous Pathogenic Factors

Tumor growth and metastasis depend on tumor microenvironment (TME) in which it exhibits the enhanced angiogenesis, matrix remodeling, and immunosuppression.[80] According to the TCM theory, the cancer occurrence is due to body deficiency and toxin accumulation.[81] The accumulated toxin as a chronic stress could force the disease development, especially carcinogenesis by influencing signaling pathways that involved in the neuroendocrine and sympathetic nervous systems and therefore elevating the downstream oncogenes expressions, this opinion was confirmed by the fact that β-adrenergic receptor (ADRB) antagonists and downstream target inhibitors show significantly anti-tumor effects.[82] TCM as a very important tumor treatment strategy has been used to treat cancers for centuries in China. Although modern medicine explains the rationale of TCM treating cancer by enhancing the immunity as well as suppressing the development and metastasis of cancer, however, it is not clear how TCM *actually* plays a role in tumors.[83] In the perspective of TCM theory, regulating TME should be the mainly therapeutical effect of TCM on tumors, which is achieved by balancing Qi, Xue, Yin and Yang to dispel dampness and resolve phlegm.[84]

Rhubarb as a classical laxative medicine has multiple traditional pharmacological actions,[85] for example, eliminating heat, purging fire, dispersing blood stasis, and so on, which is the basic application of rhubarb in various diseases.[86] Emodin, a major bioactive component of rhubarb, is rarely absorbed in intestine and can stimulate intestinal motility and peristalsis to exhibit the laxative effect by promoting the expression of aquaporin-3 and the water transport out of colon luminal.[87]

In addition, it was reported that emodin could reduce Na+/K+-ATPase to increase intestinal osmotic pressure and display an acetylcholine-like effects.[88] It is believed that the laxative effect of emodin is caused by its chemical and biological characteristics.[89] Usually, emodin enters colon luminal by an inactive glycosidic and is cleaved by the intestinal bacteria to the active aglycones, which disturb the colon epithelial cells to stimulate the underlying smooth muscle contractility and therefore exerting a laxative effect.[89] In addition, the hydroxyl groups presenting in the aromatic rings of emodin may form hydrogen and ionic bonds to cause the biological interactions of emodin with channels, transporters, receptors and enzymes.[90] The eliminating effect of emodin on poisonous pathogenic factors was confirmed by the fact that emodin could decrease uremic toxins-related Clostridium spp. and increase beneficial probiotic to improve chronic kidney disease by purgation and detoxification.[91]

To further illustrate the potential mechanism of emodin in the acceleration of poisonous elimination, a relevant network pharmacology was conducted (Fig. 3). Emodin has 46 potential targets associated with poisonous elimination, the protein-protein interaction network was showed in Figure 3a. The KEGG enrichment analysis revealed that these targets were significantly enriched in 61 poisonous elimination related pathways ($p \leq 0.05$), among which "PI3K-Akt signaling pathway", "TNF signaling pathway", "MAPK signaling pathway", "NF-kappa B signaling pathway" and "VEGF signaling pathway" are reported to be regulated by emodin.[92, 93] And some metabolic related pathways in the enrichment result, such as "central carbon metabolism in cancer", "tryptophan metabolism" and "insulin resistance", which may be related to detoxifying function of emodin. And the GO analysis revealed that these targets are participate in 77 poisonous elimination related biological process ($p \leq 0.01$). As the GO analysis exhibited, emodin could participate in a plentiful of biological processes in response to toxins, drug and external stress, for example, "response to drug", "cellular response to organic cyclic compound", "response to estradiol", "response to glucocorticoid", "response to gamma radiation", "positive regulation of fever generation", "cellular response to drug", "response to lipopolysaccharide", "cellular response to mechanical stimulus", "response to toxic substance", "response to X-ray", "oxidation-reduction process", "response to antibiotic", "response to hydrogen peroxide" and "response to wounding", which indicated that emodin may regulate multiple processes to promote the elimination of poisonous pathogenic factors.

4. Emodin Regulates System Immune Function

The immune cells could potently modulate the cancer development and metastasis,[94] hence immunotherapy has been an important treatment modality throughout oncology and lung cancer has become one of the most benefited cancers from this approach.[95, 96] However, currently, a large portion of lung cancer patients cannot benefit or transiently benefit from these immunotherapies due to immunosuppressive microenvironment (ISM).[97] TCM also advocates enhancing the immunity against cancer cells, which provides different perspectives for developing novel tumor immune suppression mechanism and new immunotherapies.[98] Unlike western medicine which only exert unidirectional immunoregulation, TCM compounds bidirectionally tune immune reaction with a change in immunosuppressive microenvironment,[99] and emodin is so. Correspondingly, Harikrishnan et al reported that emodin as a feed additive could stimulate the immune defense to enhance disease resistance function and boost hematology parameters in Clarias batrachus against Aeromonas hydrophila infection.[100]

It is well known that macrophage infiltration is associated with the severity of many types of cancers.[101] In lung cancer, tumor-associated macrophages (TAM) accumulation is positively correlated with the worse clinical outcome.[102] Usually, TAM can be educated into an M2-like phenotype after recruited by tumor cells with the secretion of growth factors and chemokines to form an ISM.[103] However, emodin has strong anti-inflammatory property and could inhibit macrophage activation through multiple targets. Iwanowycz et al previously showed that emodin could block the tumor-promoting feed forward loop between cancer cells and macrophages, decrease macrophage recruitment and M2-like polarization, and therefore suppress breast cancer growth and its lung metastasis.[104, 105] In poly I:C-induced mice RAW264.7 macrophages, emodin could reduce the expressions of IL-1α, IL-Iβ, IL-6, NO, G-CSF, GM-CSF, M-CSF, MIP-1a, MIP-

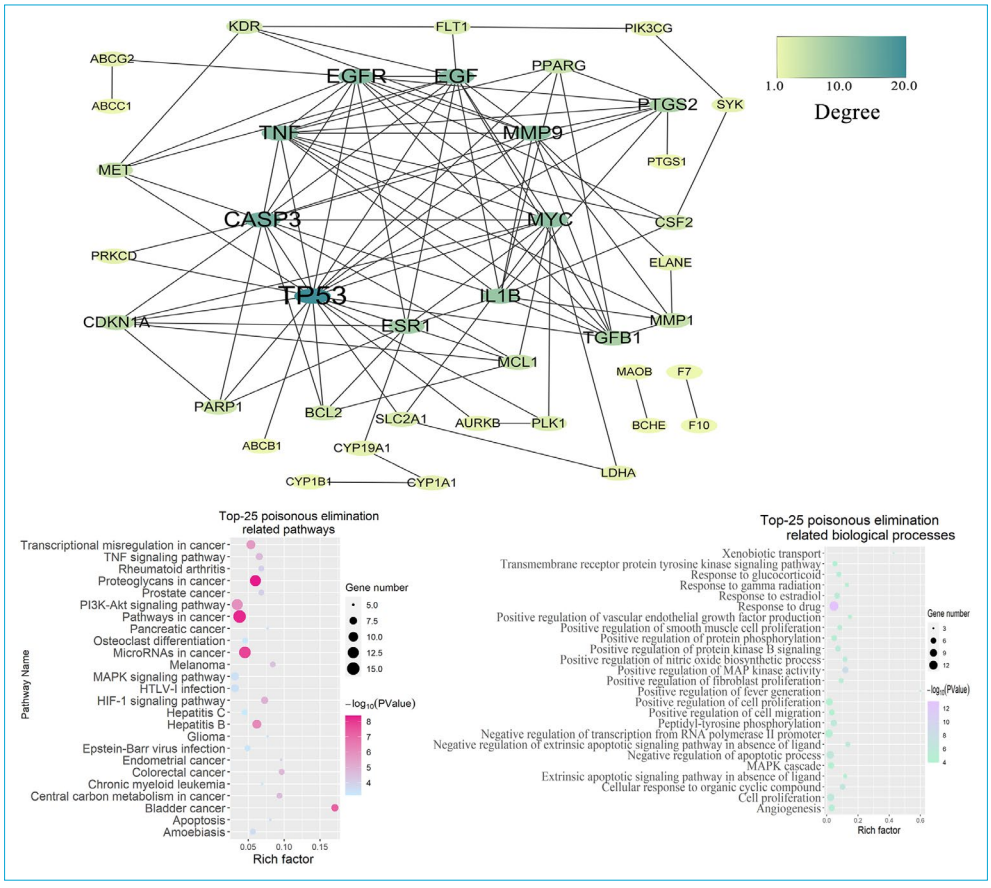

Figure 3. Potential mechanism associated with poisonous eliminating effect of emodin; **(a)** Protein-protein interaction network of potential targets associated with poisonous eliminating effect of emodin; **(b)** The potential targets involved in KEGG pathways; **(c)** The potential targets involved in biological processes.

Iβ, MCP-1, RANTES, IP-10 and MIP-2, inhibit mRNA expression of STAT1, and thus restore the macrophage viability.[106] Not only does emodin inhibit macrophage recruitment and M2 phenotype macrophage production in cancer patients,[107] and emodin could inhibit alternatively activated macrophages polarization to against asthma.[108] It is believed that emodin is able to either delay M1 polarization by suppressing NFκB/ IRF5/STAT1 signaling pathways or inhibit M2 alternative activation via inhibiting IRF4/STAT6 signaling, and therefore displaying a uniquely macrophage excessive response-suppressing effect to both M1 and M2 phenotype and keeping the macrophage in a stable state of homeostasis activation.[104]

Neutrophils and lymphocytes are another two tumor-associated stroma cells in TME, and also contribute to lung cancer growth and metastasis. Tumor cells can co-opt the expanded neutrophils and lymphocytes and educate them into an N2-like or Treg phenotype as an accomplice.[109] The anti-tumor properties of emodin are well related to cancer immunotherapy. In our previous study, emodin could selectively suppress the production of N2 neutrophil and neutrophil extracellular traps and prevent hypercoagulation and lung cancer in urethane-induced lung cancer model.[76] In an earlier study, emodin might prevent lymphocyte proliferation, regulate balance of the TH1/TH2 and TH17/Treg, and exert pro and/or anti-inflammatory action.[110] There were some studies proved that emodin could decrease inflammatory cell infiltration, reduce the levels of inflammatory cytokines, such as IL-5, IL-17, IFN-γ and so on in bronchoalveolar lavage fluid and serum, and prevent the expressions of DDL4 and Notch 1, 2, 3 in lung tissue.[111]

To further illustrate the potential mechanism associated with system immune function regulation effect of emodin, a relevant network pharmacology was conducted (Fig. 4). Emodin has 71 potential targets associated with immune function regulation, the protein-protein interaction network was showed in Figure 4a. The KEGG enrichment analysis revealed that these targets were significantly enriched in 63 immune function related pathways ($p \leq 0.05$), among which "MicroRNAs in cancer", "PI3K-Akt signaling pathway", "NF-kappa B signaling pathway", "TNF signaling pathway", "p53 signaling pathway",[112] "MAPK signaling pathway" were reported to be regulated by emodin. And the GO analysis revealed that these targets are participate in 108 immune function regulation related biological process ($p \leq 0.01$), among which "positive regulation of MAP kinase activity", "positive regulation of nitric oxide biosynthetic process", "inflammatory response", "re-

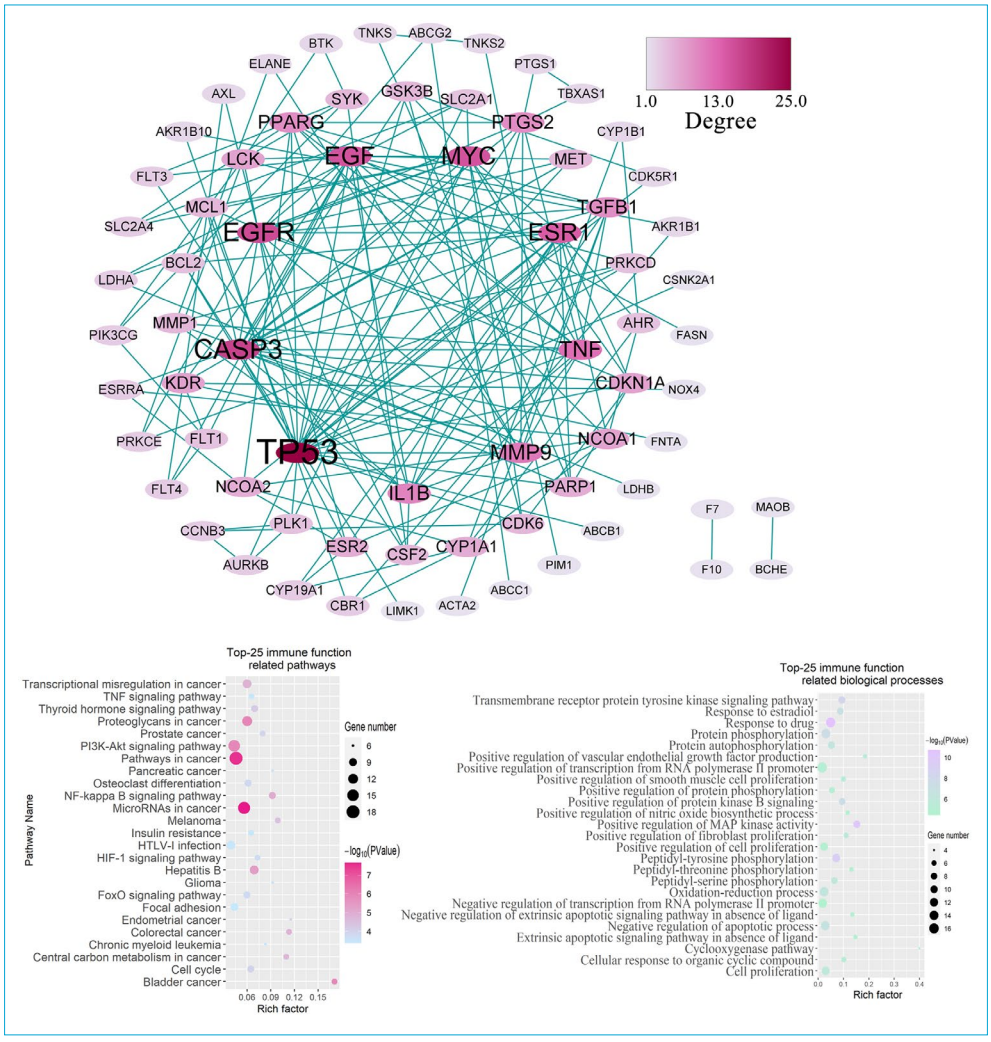

Figure 4. Potential mechanism associated with immune regulating effect of emodin; **(a)** Protein-protein interaction network of potential targets associated with immune regulating effect of emodin; **(b)** The potential targets involved in KEGG pathways; **(c)** The potential targets involved in biological processes.

sponse to lipopolysaccharide" and so on are reported to be regulated by emodin.

5. Published Researches on the Effects of Emodin on Lung Cancer

We searched and summarized the research reports on the effects of emodin on lung cancer published since 2005, including in vivo and in vitro experiments. The direct targets and downstream effects of emodin and the experimental model and cell lines had shown in Table 1.

As repots, emodin can not only inhibit the progression of lung cancer, but also affect the immune environment of the lung to treat lung cancer. It has multiple-targets, such as NF-κB, CXCR4, Bax, MKK1/2, ERK1/2 and so on, which gives emodin the ability to regulate directly or indirectly the biological processes of cell cycle, cell vitality, oxidative stress and so on in lung cancer cells. Among these targets and pathways that emodin regulated, AKT, MAPK, ERK and MYC and NF-κB signal pathway were predicted by network pharmacology above, which further proves the accuracy of network pharmacology. However, there are still plentiful contents in the analysis needed to be verified, for example, HIF-1 signal pathway, ERBB family signaling, FOXO signaling and so on, they have great potential in cancer treatment.

Future Prospect

Traditional Chinese medicine (TCM) has been treating tumors for more than 2000 years and is widely accepted in clinical cancer treatment in Chinese hospitals at present. Although TCM has multifunctional therapeutic effect in cancer treatment and gradually showed its superiority in clinical practice,[125] it is only an alternative treatment for

Table 1. The reported mechanisms of emodin treating lung cancer

Reference	Direct target	Downstream effect	Model/Cell lines
113	sPLA2-IIa and NF-κB signal pathway ↓	Inducing apoptosis	A549, H1650, H460, H1975, PC9, H1299
114	TWIST, SNAI1, SNAI2and NF-κB ↓	Reversing chemoresistance and inducing apoptosis and cell cycle arrest	H69, A549, H446
115	P2Y receptors ↓	Inhibiting ATP-induced proliferation, migration and EMT and ATP-activated Ca 2+ dependent NF-κB signal pathway	A549
116	CXCR4 ↓	Inhibiting invasion and migration	A549
117	Bax and active caspase 3 ↑ Bcl-2, p-Akt and p-ERK ↓	Inducing paclitaxel-induced apoptosis	A549
118	ERCC1, Rad51 ↓	Suppressing cell proliferation	SK-MES-1, A549
119	ROS ↑; ERK, AKT ↓	Inducing elevation of Bax, reduction of Bcl-2 levels, release of cytochrome c and activation of caspase-2, -3, and -9, simultaneously, mediated apoptosis	A549
120	Phosphorylated MKK1/2 and ERK1/2 ↓	Reducing cell viability by inhibiting expression of ERCC1 and Rad51	H1650, A549, H520, H1703
20	P53 protein aggregates ↓ LC3 mRNA expression↑	Increasing autophagy level in A549 cells	A549, HaCaT
121	ROS ↑	Inducing release of cytosolic cytochrome c by increasing the accumulation of p53 and Bax to enhance apoptosis	A549
112	HAS2 ↓	Regulating cyclins to inhibit the proliferation	A549, H520, H1975, H460, H1299
113	TRIB3/NF-κB signaling ↑	Inducing apoptosis by increasing endoplasmic reticulum stress	A549, H1299
123	FASL ↑ C-MYC ↓	Inducing apoptosis by up-regulation of FASL expression and disable damage repairing by down-regulation of C-MYC expression	A549
76	Cit-H3 and PAD4 ↓	Preventing hypercoagulation and lung carcinogenesis by regulating neutrophil phenotypes	Lewis lung cancer allograft model, urethane-induced lung carcinogenesis model

cancer at the present time due to the arcane theory and complex mechanism.[81] Unlike modern medicine which is based on disease pathology, TCM is based on syndrome differentiation which would benefit the patients with personalized conditions.[84] According to the TCM theory, disequilibrium between Yin and Yang is the fundamental principle of all diseases, TCM can restore the harmony of Yin and Yang to alleviate disease symptoms which are the *warning signs* of visceral dysfunction.[125] As show in Figure 5, emodin is a multiple target and multifunctional compound, which conform a basic concept of TCM treating cancer in which disease treatment should systematically regulate the body to eliminate the disturbance of Yin and Yang rather than block *warning signs to ignore* these malfunctions.[84]

Emodin has anti-ulcer, anti-inflammatory,[126] hepatoprotective,[127] muscle relaxant, immunomodulation and antifibrotic function besides antineoplastic activity.[128] In TCM theory, lung and large intestine are as external-internal relations, the use of the laxative medicine emodin for lung cancer treatment is reasonable. However, based on the literature, emodin could also lead to hepatotoxicity,[129, 130] kidney toxicity and reproductive toxicity when high doses and long-term drug delivery,[131] whereas low doses and short-term drug delivery might result in liver protection.[37] The effects of emodin on intestinal flora and micro-ecological reestablishment have attracted increased attention, which has highly potential to prevent cancer development in recent years.[132, 133] Although purgative potential is a basic effect of emodin on many diseases, emodin long-lasting delivery can also cause electrolyte disturbance and fluid imbalance, especially drug abuse. With the development of system biology, just like the great discovery of artemisinin, a popular anti-malarial drug extracted from the Chinese herbal medicine, scientifically regarding the vague molecular targets and real mechanisms would contribute to the widespread acceptance of emodin not only as an anti-cancer drug but also as a promising health-promoting drug in clinical application.

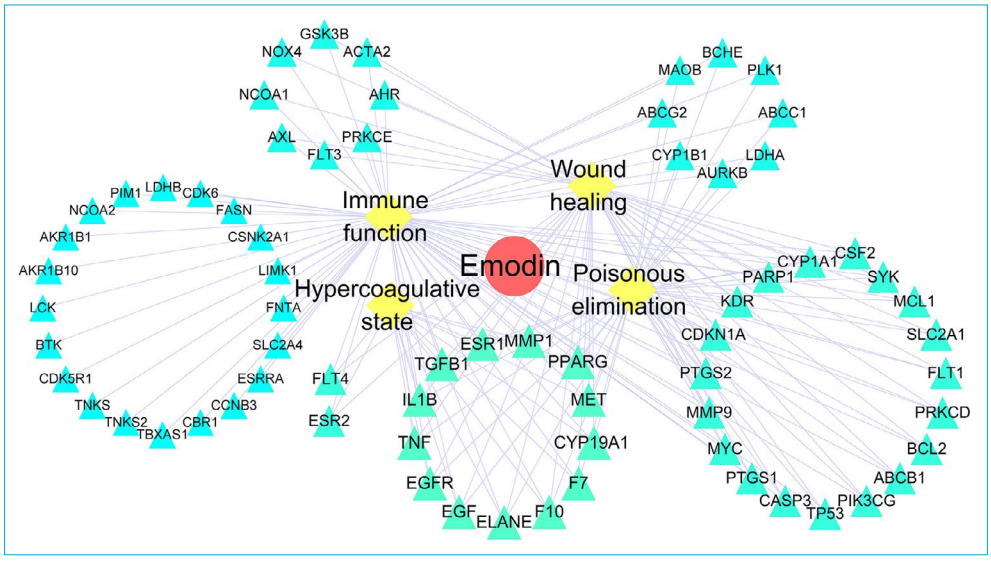

Figure 5. The potential functions and targets of emodin, the yellow nodes are the potential functions of emodin and the green nodes are the predicted targets of emodin.

Disclosures

Ethics Committee Approval: Experiments were approved by the Henan University Animal Care and Use Committee (Permission number: HUSAM 2021-069), and conducted in accordance with the ethical standards and national guidelines.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Data availability statement: All datasets generated for this study are included in the article.

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