Original Article

Exploring the Molecular Mechanism of *Radix Astragali* on Colon Cancer Based on Integrated Pharmacology and Molecular Docking Technique

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Abstract

Objective: The objective of this study was to study the mechanism of *Radix Astragali* on colon cancer by integrated pharmacology and molecular docking technique. **Methods:** Integrative pharmacology-based research platform of traditional Chinese medicine (TCMIP) V2.0 was used to obtain the chemical components and corresponding targets of *Radix Astragali* and the target information of colon cancer to create the main target network of drugs and diseases. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was carried out using Hiplot website, and the interaction network of "Traditional Chinese Medicine-component-target-pathway" was established, and molecular docking with main targets was carried out for the key components. **Results:** Twenty-seven chemical constituents of *Radix Astragali*, their 254 corresponding targets, and 44 colon cancer-related targets were obtained. Through proteins interacting, 70 nodes were obtained as core targets. GO analysis showed that it mainly acts on lipid metabolism, nuclear receptor activity, phagocytic cup, etc. KEGG pathway analysis showed that it was mainly enriched in the estrogen signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway, etc. The multidimensional network, quantitative estimate of the drug, and molecular docking showed that the main targets are AKT1, BCL2, and CDK6, and the key components involved are kumatakenin, astragaloside VIII, and choline. **Conclusion:** Kumatakenin, Astragaloside VIII, Choline and other compounds of Radix Astragali may affect colon cancer by acting on AKT1, BCL2 and other targets, thereby regulating estrogen signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway and so on. Those will provide theoretical reference for future research on the material basis and mechanism of its pharmacodynamics.

Keywords: Colon cancer, integrated pharmacology, mechanism, *Radix Astragali*

Introduction

Colon cancer is a malignant tumor occurring in the colon and rectum. According to the US cancer data in 2018,[1] the incidence of colon cancer is the third highest, with 9% of men and 7% of women. With the development of the economy, China's living standard has greatly improved, and people's food intake has changed. Meanwhile, the aging of the population is becoming increasingly serious, and the number of colon cancer patients is also increasing. According to the 2015 China Cancer[2] reported, 376,000 new colon cancer patients and 191,000 deaths were reported in China, ranking fifth. The incidence of colon cancer in the rural areas is much lower than that in urban areas, and the overall incidence has significantly increased in recent years. *Radix Astragali* has the functions of tonifying the middle and nourishing qi, solidifying the surface and benefiting water, supporting sepsis, and strengthening muscles.[3,4] It is used for symptoms such as refractory ulcer and deficiency.[5] *Radix Astragali* contains polysaccharides, saponins, flavonoids, amino acids, and sterols. Modern pharmacological studies have found

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that Radix Astragali has anti-tumor, cardiovascular, improve immune function, lung function protection, kidney protection, liver injury protection, intestinal function protection, blood pressure regulation, anti-aging, prevention of osteoporosis, antioxidant stress, peritoneum protection, anti-radiation protection, retinal ganglion cells and other characteristics. Recent studies have found that *Radix Astragali* can inhibit colon cancer proliferation.[6,7] However, the mechanism of its relationship regarding colon cancer is still unclear. The computational platform for integrated pharmacology of Traditional Chinese Medicine (TCMIP; www.tcmip.cn)[8] includes a database of prescriptions, herbs, ingredients, and disease/symptom targets. This platform was used to analyze the interaction network of TCM components, targets and diseases, and explore its pharmacodynamic substance basis and mechanism of action.[9] Based on TCMIP platform, this study established the mechanism network of *Radix Astragali* for colon cancer effects, providing scientific basis for exploring more application scope of *Radix Astragali.*

Methods

Collection of chemical constituents and related targets of Radix Astragali

Traditional Chinese Medicine (TCM) database based on TCMIPV2.0 (http://www.tcmip.cn/TCMIP/index.php/) for the composition of *Radix Astragali*. The chemical composition of *Radix Astragali* was scored for similarity with known drugs in the database of Chinese medicinal materials, and corresponding targets were collected. We used the target with the default score ≥0.80 as the targets of *Radix Astragali* and established the database of *Radix Astragali* chemical compositions and relevant targets.

Colon cancer targets collection

We searched the keyword "Colon Cancer" in the disease-related molecular library of TCMIP V2.0 to build a colon cancer target database.

Establishing main targets network and enrichment analysis of GO function and KEGG pathway

The target interaction information of *Radix Astragali* and colon cancer was constructed based on the STRING database (http://string-db.org/, V11.0). The organism was set as "Homo sapiens," the minimum interaction score was >0.4, the remaining parameters were kept as the initial setting, and the results were derived. Node degree, betweenness, and closeness were taken as parameters to analyze the target of which degree is greater than the median and further calculate the betweenness and closeness. The nodes, whose three Eigen values were all greater than the median and their interaction relationships, were retained and imported into Cytoscape3.8.0 software (Leroy Hood laboratory, Trey Ideker laboratory, Bruce Conklin laboratory, Chris Sander laboratory, Benno Schwikowski laboratory and other research units developed an open source bioinformation analysis software) to construct the core target network of *Radix Astragali* and colon cancer. Using Hiplot (https://hiplot.com.cn/advance) in the GO/KEGG analysis module, to get the core target of the GO function analysis and KEGG pathway enrichment analysis. Then, the related targets and components involved in the regulation of the first 20 pathways in *Radix Astragali* are considered key compounds and main targets.

Quantitative evaluation of main components of Radix Astragali

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) levels of key chemical components were retrieved using the Chinese medicine component database of TCMIP V2.0 with 0 representing "Good," 1 representing "Moderate," 2 representing "Low," and 3 stands for very low. Quantitative estimate of drug-likeness (QED) uses eight indicators: molecular weight, oil-water partition coefficient (ALOGP), hydrogen bond receptor number (HBAs), hydrogen bond donor number, molecular polar surface area, rotable bond number (ROTBs), aromatic ring number (AROMs), and number of alart structures (ALERTs), respectively. The QED score is calculated according to the formula $QED = \exp(1/n\sum_{i=1}^{n}Ind_i)$: Weak ($QED < 0.49$), moderate ($0.49 \leq QED \leq 0.67$), and good ($QED > 0.67$). QED scores were used to evaluate the quasi-drug grade.[10] Compared with traditional pharmacokinetic parameters, QED scores include the molecular structure, physicochemical properties, and ADME properties of compounds and provide a more comprehensive description of the medicinal properties of compounds.

Molecular docking analysis of main targets and related *Radix Astragali* components in colon cancer

The top five main proteins that were involved in the first 20 pathways were selected, with the effects of the colon cancer directly noted using the CB-Dock (http://cao.labshare.cn/cb-dock/) for docking with targets. *Radix Astragali* root key elements were used to assess their combined with the corresponding protein.

Results

Chemical constituents and targets of Radix Astragali

Based on TCMIP V2.0, 27 chemical constituents and related 254 targets of *Radix Astragali* were obtained.

The core target analysis

Based on TCMIPV2.0 disease-related molecular library, 44 colon cancer-related targets were obtained. The interaction network between the corresponding targets of *Radix Astragali* and colon cancer-related targets was constructed based on the STRING database, and 70 core targets were obtained. Among them, there were 56 targets of *Radix Astragali* and 16 targets related to colon cancer, and there were two common targets of both, as shown in Table 1.

GO function analysis and KEGG pathway enrichment analysis

GO and KEGG enrichment analyses were performed on 70 core targets. The result showed that GO function analysis conducted in-depth analysis of the top 10 items in the descending

order of *P* values according to biological process, molecular function, and cell composition; and the biological processes involved, included regulation of lipid metabolic process, small molecule metabolic processing, and monooxygenase activity. The molecular functions involved included nuclear receptor activity and chromatin binding and DNA-binding transcription factors. Cell composition included phagocytic cup, membrane raft, and synaptonemal complex, all of which are related to DNA transcription and translation, as well as cell metabolism, as shown in Table 2. For in-depth analysis, the top 20 KEGG pathway enriched *P* values from small to large were selected. The results showed that the main targets were mainly enriched in estrogen signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway, and thyroid hormone signaling pathway, as shown in Figure 1.

Table 1: Common targets of *Radix Astragali* and colon cancer

Tagets	Uniport number	Name
MTHFR	P42898	Methylenetetrahydrofolate reductase
HDAC2	Q92769	Histone deacetylase 2

Table 2: Analysis of gene ontology function of core target of colon cancer affected by *Radix Astragali*

Category	Function	*P*
Biological process	Cellular response to lipid	<0.001
	Response to steroid hormone	<0.001
	Cellular response to organic cyclic compound	<0.001
	Regulation of lipid metabolic process	<0.001
	Gland development	<0.001
	Intracellular receptor signaling pathway	<0.001
	Aging	<0.001
	Regulation of small molecule metabolic process	<0.001
	Positive regulation of small molecule metabolic process	<0.001
	Regulation of monooxygenase activity	<0.001
Molecular function	Nuclear receptor activity	<0.001
	Ligand-activated transcription factor activity	<0.001
	Chromatin binding	<0.001
	RNA polymerase II-specific DNA-binding transcription factor binding	<0.001
	DNA-binding transcription factor binding	<0.001
	Steroid hormone receptor activity	<0.001
	Nuclear receptor binding	<0.001
	Steroid binding	<0.001
	Drug binding	<0.001
	Transcription coactivator binding	<0.001
Cell composition	Phagocytic cup	<0.001
	Membrane raft	<0.001
	Membrane microdomain	<0.001
	Membrane region	<0.001
	Synaptonemal complex	<0.001
	Synaptonemal structure	<0.001
	DNA repair complex	<0.001
	Myelin sheath	<0.01
	RNA polymerase II transcription regulator complex	<0.01
	Extrinsic component of membrane	<0.01

Multidimensional network analysis

The first 20 pathways of KEGG enrichment by Cytoscape3.8.0 were used to construct a multidimensional network of "TCM-compound-target-pathway" [Figure 2]. The network involves nine key compounds and 31 main targets. The nine key components regulate the 31 main targets such as tumor necrosis factor, HDAC2, interleukin (IL-6), and methylenetetrahydrofolate reductase (MTHFR), which are involved in estrogen signal pathway, c-type lectin receptor

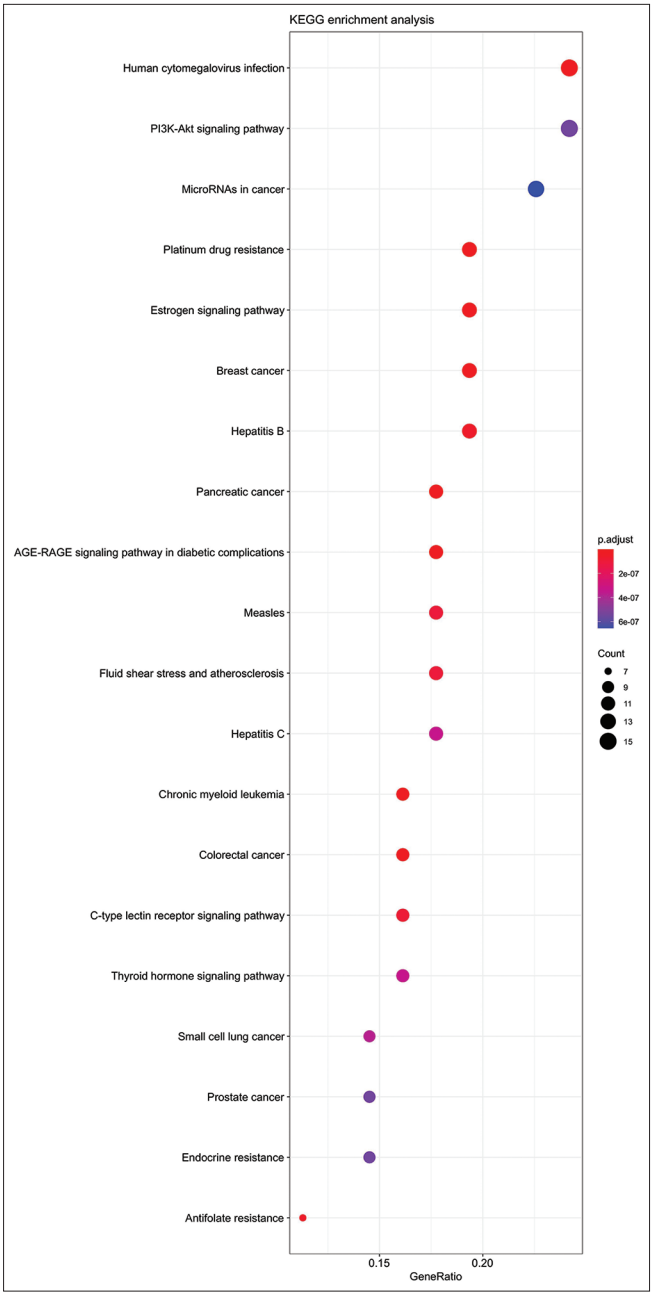

Figure 1: KEGG enrichment analysis of core targets of *Radix Astragali* for colon cancer affection

signal pathway, and PI3K-Akt signal pathway. AKT1, BCL2, and CASP3 also participate in these pathways. Different components of TCM regulate their corresponding targets and interfere with different signal pathways. For example, kumatakenin acts on AKT1, regulates colon cancer, estrogen signaling, c-type lectin receptor signaling, and PI3K-Akt signaling.

Quantitative evaluation of absorption, distribution, metabolism, excretion, and toxicity level and quasi-medicinal properties of key components

Based on the multidimensional network of "TCM-component-target-pathway," the ADMET level and QED of TCM key components acting on main targets were evaluated, and the results are shown in Table 3. Then, according to the comprehensive consideration of QED evaluation criteria and ADMET absorption level, those with QED ≥0.49 or ADMET absorption level 0 were selected for the analysis, and the results showed that the drug-like properties and absorption level of kumatakenin were relatively good.

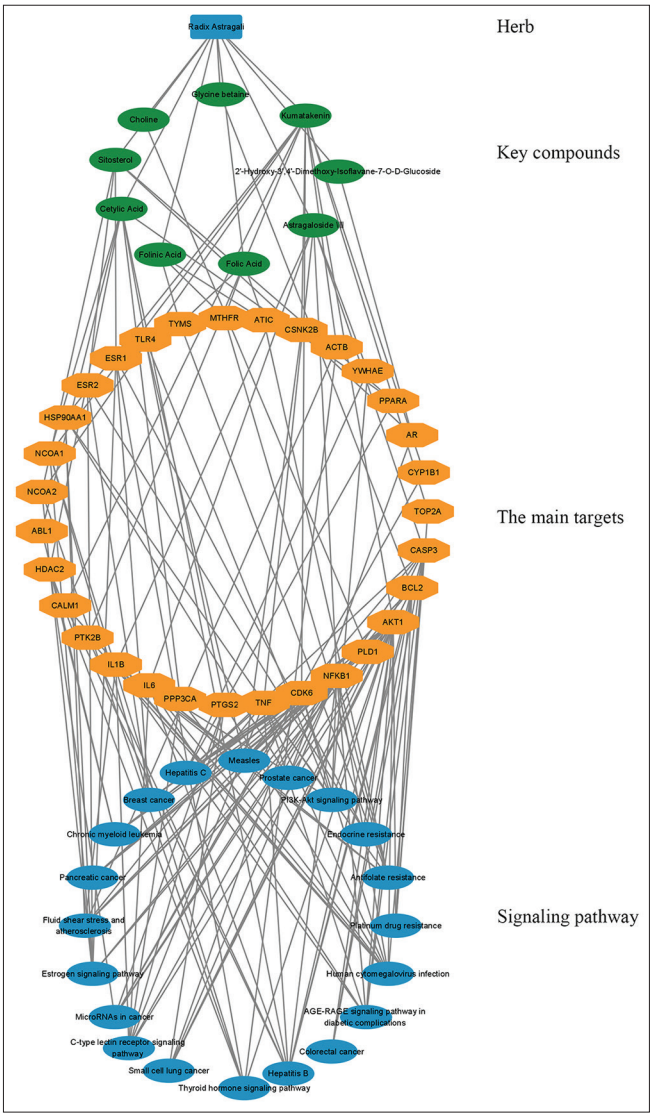

Figure 2: Effect of *Radix Astragali* on colon cancer multidimensional network of "Traditional Chinese Medicine-component-target-pathway"

Molecular docking analysis of main targets and *Radix Astragali* components in colon cancer

The molecular docking results based on the first five main targets and the key components of *Radix Astragali* are shown in Table 4. Apparently, the binding degree of astragaloside VIII to these main targets is the best, the binding degree of sitosterol to AKT1 and CDK6 is the best, and the binding degree of astragaloside VIII to BLC2 and NFKB1 is the best. The best combination with CASP3 is astragaloside VIII, and sitosterol is shown in Figure 3.

Discussion

The occurrence of colon cancer is caused by the joint action of various factors.[11] In addition, age, gender, family history of colon cancer, inflammatory bowel disease,[12] smoking, excessive alcohol consumption, excessive intake of red meat, obesity,[13] and diabetes have all been proven to be closely

Table 3: Absorption, distribution, metabolism, excretion, and toxicity level analysis and quantitative estimate of drug-likeness evaluation of key components of *Radix Astragali*

Compounds	QED scores	Drug-like grade	ADMET levels
Kumatakenin	0.904	Good	0
Astragaloside VIII	0.112	Weak	3
Glycine betaine	0.361	Weak	3
Choline	0.398	Weak	2
Cetylic acid	0.391	Weak	1
Sitosterol	0.435	Weak	3
4-Hydroxycoumarin, folinic acid	0.189	Weak	3
3-Hydroxycoumarin, folic acid	0.264	Weak	3
2'-Hydroxy-3',4'-Dimethoxy-Isoflavane-7-O-D-glucoside	0.349	Weak	2

ADMET: Absorption, distribution, metabolism, excretion, and toxicity, QED: Quantitative estimate of drug-likeness

Table 4: Docking results of the first five main targets and *Radix Astragali* components

Compounds	Target				
	CDK6	AKTI	NFKB1	BLC2	CASP3
Kumatakenin	−8.1	−8.6	−5.9	−6.6	−7.6
Astragaloside VIII	−8.0	−9.9	−8.8	−8.3	−9.4
Glycine betaine	−3.5	−3.7	−3.3	−3.6	−3.5
Choline	−3.1	−3.6	−3.2	−3.8	−3.2
Cetylic acid	−5.7	−6.6	−4.5	−4.6	−5.8
Sitosterol	−9.8	−10.6	−6.5	−6.4	−9.4
4-Hydroxycoumarin, folinic acid	−8	−9.8	−7.5	−7.7	−9.2
3-Hydroxycoumarin, folic acid	−8.4	−9.7	−7.3	−7.3	−9.3
2'-Hydroxy-3',4'-Dimethoxy-Isoflavane-7-O-D-glucoside	−8.1	−9.5	−6.6	−6.7	−9.3

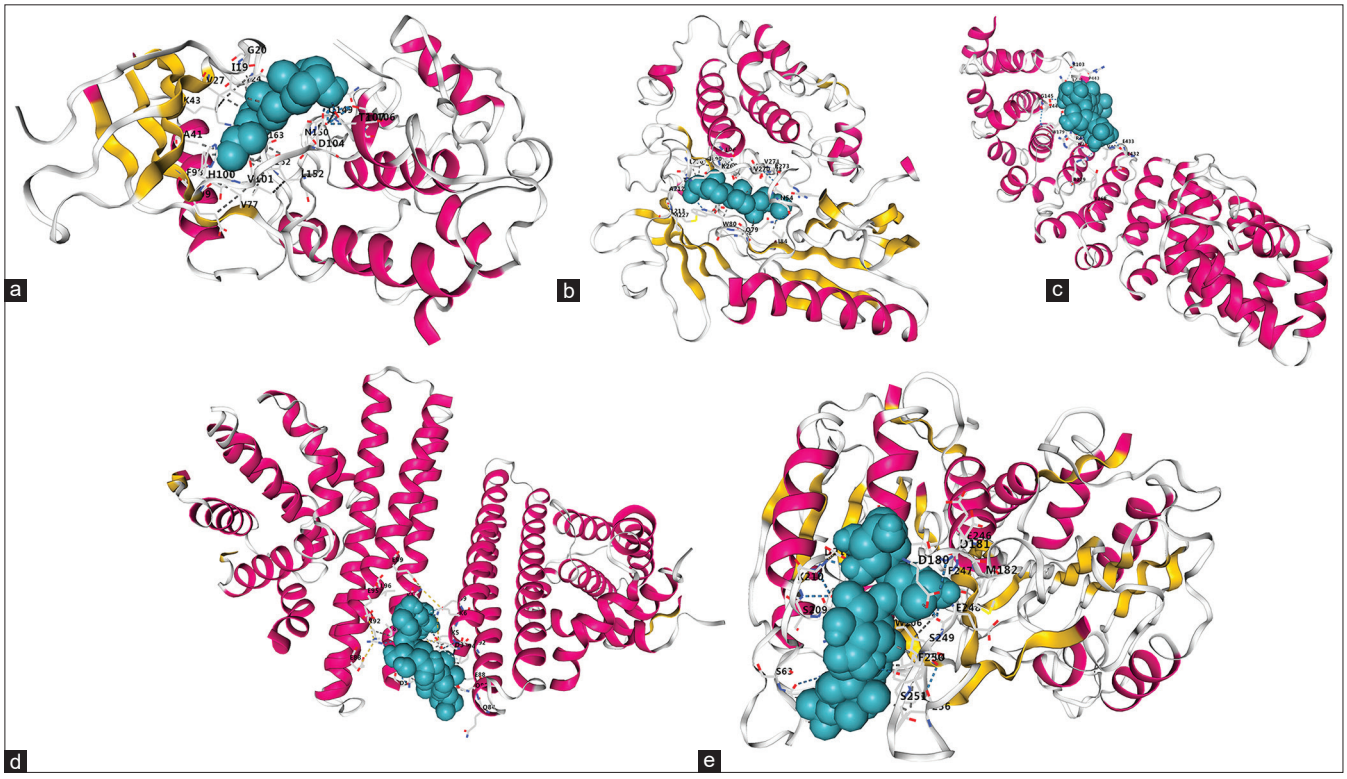

Figure 3: The best schematic diagram of *Radix Astragali* components binding to the first five main targets. (a) CDK6 is combined with sitosterol, (b) AKT1 is combined with sitosterol, (c) NFKB1 is combined with astragaloside VIII, (d) BLC2 is combined with astragaloside VIII, (e) CASP3 is combined with astragaloside VIII

related to the occurrence of colon cancer. Young patients with colon cancer apparently present with abdominal pain, blood in the stool, weight loss, and changes in defecation habits. Based on TCMIPV2.0, this study explored the possible mechanism of action, compound composition, and related targets of *Radix Astragali* affecting colon cancer and intuitively demonstrated the multicomponent, multi-pathway, and multi-target integrated regulation mode of *Radix Astragali* affecting colon cancer.

A total of 27 chemical constituents of *Radix Astragali* were obtained by TCMIPV2.0, which correspond to 254 targets. Through the protein interaction network between *Radix Astragali* and colon cancer was constructed based on the STRING database, and 70 core targets were obtained. Among them, there were 56 targets of *Radix Astragali* and 16 targets for colon cancer, and there were two common targets, namely MTHFR and HDAC2, suggesting that these targets may be closely related to the effect of *Radix Astragali* on colon cancer. After analysis, the GO function of the core targets showed that the biological processes involved included regulation of lipid metabolism, regulation of small molecule metabolism, regulation of monooxygenase activity, and so on. The molecular functions involved included nuclear receptor activity, binding chromatin, and binding DNA-binding transcription factors, among others. The cell components involved included phagocytic cell cup, membrane raft, synaptic complex, and others, which were all related to the transcription and translation of DNA and cell metabolism. KEGG pathway enrichment analysis showed that it was mainly concentrated in the estrogen signal pathway, C-type lectin receptor signal pathway, PI3K-Akt signal pathway, thyroid hormone pathway, and others.

In the estrogen signaling pathway, *Radix Astragali* is involved in AKT1, BCL2, ESR1, ESR2, and HSP90AA1 and is also involved in the cell cycle, cytoplasmic signaling, pro-apoptotic proteins, and membrane composition. Estrogen receptors alpha (ERα) and ERβ play opposite roles in cell proliferation, apoptosis, and migration by inducing different transcriptional responses, thus affecting the occurrence and development of cancer differently. Estrogen promotes the development of colon cancer through mucosal damage and inflammatory response.[14] Activation of intestinal ER-β (/ESR2) contributes to the formation of a more favorable microbiome, which inhibits the development of colon cancer.[15] ERs regulate gene expression through the interaction of proteins with other DNA-binding transcription factors in the nucleus. Membrane-associated ERs mediate the nongenomic effects of estrogen, leading to changes in protein function and regulation of gene expression in the cytoplasm.[16]

In the C-type lectin receptor signaling pathway, *Radix Astragali* participates in the targeting of PTGS2, IL1B, IL6, and NFKB1, among which PTGS2, IL1B, and IL-6 regulate the differentiation of Th1 and Th17 cells, while NFKB1 regulates the differentiation of Th1 and Th2 cells, thus regulating the

immune function of the body. IL6 may influence colon cancer metastasis by enhancing host immunity. *Radix Astragali*, by regulating the C-type lectin receptor signaling pathway, affects the body's autoimmunity and influences the development of colon cancer.

In the PI3K-Akt signaling pathway, *Radix Astragali* participates in AKT1, NFKB1, CDK6, and YWHAE. AKT1 may be a key regulator of epithelial-mesenchymal transition in colon cancer cells.[17] Activating the expression of TLR4, HSP09AA1, NFKB1 and YWHAE promoted colon cancer cell survival, and promoting CDK6 expression blocked colon cancer cell cycle. Elevated AKT1 levels can promote colon cancer progression *in vivo* and *in vitro*.[18] In addition, the PI3K-Akt signal transduction pathway is out of control in colon cancer patients.[19] *Radix Astragali* may participate in the regulation of PI3K-Akt signaling pathway and affect colon cancer.

In the thyroid hormone pathway, *Radix Astragali* participates in ESR1, HDAC2, and NCOA2. Thyroid hormone controls the proliferation and differentiation of colon cancer stem cells.[20] ESR1 can promote gene expression and cell proliferation, while NCOA2 and HDAC2 can regulate DNA expression. HDAC2 belongs to a family of histone deacetylases that act by forming large multiprotein complexes and are responsible for the deacetylation of lysine residues in the n-terminal regions of core histones (H2A, H2B, H3, and H4). HDAC2 binds to many different proteins to form transcriptional repressor complexes, including the mammalian zinc-finger transcription factor YY1, which plays an important role in transcriptional regulation, cell cycle progression, and developmental events. Studies have shown that when the expression of HDAC2 is inhibited, the proliferation of colon cancer cells is also inhibited and accompanied by apoptosis.[21] In addition, targeting the P300/YY1/HDAC2 axis plays a role as a tumor suppressor in colon cancer, which contributes to the treatment of colon cancer.[22] *Radix Astragali* affects the proliferation of colon cancer cells by regulating DNA transcription and expression.

The multidimensional network of "TCM-component-target-pathway" of *Radix Astragali* affecting colon cancer can be seen in the relationship between each component. Different components of *Radix Astragali* act on different targets, such as AKT1, BCL2, HDAC2, and IL-6, and affect diseases by affecting different pathways. The pathways involved in colon cancer may be the regulation of estrogen signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway, and thyroid hormone pathway. Through QED evaluation of key compounds, kumatakenin was found to have relatively good medicinal properties and absorption levels. Through molecular docking, astragaloside VIII had the best binding degree to key targets. It is speculated that these substances play an important role in the process of influencing colon cancer.

Conclusion

In this study, the mechanism of *Radix Astragali* affecting colon cancer was predicted and analyzed based on the integrated pharmacology platform. Kumatakenin, astragaloside VIII, choline, and other components in *Radix Astragali* may regulate the estrogen signaling pathway, C-type lectin receptor signaling pathway, PI3K-Akt signaling pathway, and thyroid hormone pathway by acting on AKT1, BCL2, and other targets. It provides a theoretical reference for the future study of its pharmacodynamic substance basis and mechanism of action.

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Conflicts of interest

There are no conflicts of interest.

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