Clinical and Translational Research

Screening of traditional Chinese medicine monomers as ribonucleotide reductase M2 inhibitors for tumor treatment

Ya-Ya Qin, Song Feng, Xiao-Dong Zhang, Bin Peng

Ya-Ya Qin, Xiao-Dong Zhang, Department of Neurology, Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan Province, China
Song Feng, Bin Peng, School of Basic Medicine, North Sichuan Medical College, Nanchong 637000, Sichuan Province, China

Corresponding author: Bin Peng, MD, Professor, School of Basic Medicine, North Sichuan Medical College, No. 234 Fujiang Road, Shunqing District, Nanchong 637000, Sichuan Province, China. binpeng01@sina.com

Abstract

BACKGROUND
Ribonucleotide reductase (RR) is a key enzyme in tumor proliferation, especially its subunit-RRM2. Although there are multiple therapeutics for tumors, they all have certain limitations. Given their advantages, traditional Chinese medicine (TCM) monomers have become an important source of anti-tumor drugs. Therefore, screening and analysis of TCM monomers with RRM2 inhibition can provide a reference for further anti-tumor drug development.

AIM
To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2.

METHODS
The Gene Expression Profiling Interactive Analysis database was used to analyze the level of RRM2 gene expression in normal and tumor tissues as well as RRM2's effect on the overall survival rate of tumor patients. TCM monomers that potentially act on RRM2 were screened via literature mining. Using AutoDock software, the screened monomers were docked with the RRM2 protein.

RESULTS
The expression of RRM2 mRNA in multiple tumor tissues was significantly higher than that in normal tissues, and it was negatively correlated with the overall survival rate of patients with the majority of tumor types. Through literature mining, we discovered that berberine, ursolic acid, gambogenic acid, cinobufagin, quercetin, daphnetin, and osalmide have inhibitory effects on RRM2. The results of molecular docking identified that the above TCM monomers have a strong binding capacity with RRM2 protein, which mainly interacted through...
hydrogen bonds and hydrophobic force. The main binding sites were Arg330, Tyr323, Ser263, and Met350.

CONCLUSION
RRM2 is an important tumor therapeutic target. The TCM monomers screened have a good binding capacity with the RRM2 protein.

Key Words: Tumor; Ribonucleotide reductase M2 inhibitor; Traditional Chinese medicine; Monomer; Molecular docking; Literature mining

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Core Tip: Tumors seriously threaten human life and health. In our work, we found that ribonucleotide reductase M2 (RRM2) is highly expressed in most tumor tissues, and is related to poor prognosis. Seven traditional Chinese medicine monomers with good binding ability to RRM2 were identified, and their binding sites were summarized and analyzed. Those will provide ideas for the development of anti-tumor drugs with RRM2 inhibition in the future.

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INTRODUCTION
The tumor is a major contributor to endangering human health. In terms of disability-adjusted life years, it is only second to cardiovascular disease. The World Health Organization predicts that there will be a global increase in new tumor cases of more than 50%, from 18 million in 2018 to 27 million in 2040[1]. In addition to conventional surgical resection, drug adjuvant therapy still occupies a considerable part in the treatment of tumors. Although numerous chemotherapy medications have been developed, the majority of them have more or less side effects and some are rather pricey. Since natural chemicals are safer, cheaper, and more effective than synthetic ones, there has been an increasing interest in finding medications to prevent and cure tumors from natural compounds[2].

Ribonucleotide reductase (RR), the only multi-subunit enzyme existing in all biological cells that can catalyze the reduction of ribonucleotides to corresponding deoxyribonucleotides, is the rate-limiting enzyme of DNA synthesis. By regulating and balancing the content of different deoxyribonucleic acids (dNTPs) in the cell cycle, RR is mainly involved in DNA replication and repair, which is crucial for controlling cell proliferation and preserving genomic stability[3,4]. Human RR is composed of two large subunits M1 and two small subunits M2 (RRM2)[5]. Since RRM2 has the ability to regulate and catalyze substrates, the enzymatic activity of RR is primarily controlled by RRM2[6]. The tumor is a highly invasive disease, the tumor cell proliferation requires the participation of a large number of dNTPs[3]. Studies have found that most tumor cells express more RR than normal cells do. The overexpression of RRM2 is related to tumor malignancy, invasion, metastasis, drug resistance, and autophagy[7-9]. Inhibiting or reducing the expression of RRM2 may improve tumor patients’ disease progression and prognosis, and lengthen their survival[10].

According to the target and mechanism of action, RRM2 inhibitors are roughly divided into gene expression regulators and protein inactivators. The gene expression regulators include R2 antisense inhibitors and siRNA inhibitors, whereas free radical scavengers, iron chelators, and iron mimics fall under the category of protein inactivators[11]. Due to a wide range of pharmacological properties, some traditional Chinese medicine (TCM) monomers have also been used as RRM2 inhibitors for research. Through literature mining, we found multiple TCM monomers that have inhibitory effects against RRM2 in tumors. However, there are few studies on their interaction sites. This paper aims to elucidate the relationship between RRM2 and malignant tumors and the prognosis of tumor patients, and then to screen out potential anti-tumor TCM monomers with good binding ability to RRM2. Through the analysis of their main binding sites, some thoughts for the development of new anti-tumor drugs with RRM2 inhibition are provided.
MATERIALS AND METHODS

Tumor patients’ data acquisition
Through the Expression Profiling Interactive Analysis database (GEPIA) (http://gepia.cancer-pku.cn), we analyzed and obtained the mRNA level of the RRM2 gene in normal tissues and tumor tissues, as well as its effect on the overall survival rate of tumor patients. All tumor abbreviations were listed in Table 1.

Literature mining
PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) and the China National Knowledge Infrastructure database (CNKI, https://www.cnki.net) were used to retrieve and download the articles related to TCM monomers acting on RRM2 targets. Subsequently, the application of TCM monomers in tumors was summarized and analyzed one by one.

Molecular docking
According to the small molecule CAS number from the PubChem database, we downloaded the 3D structure of TCM monomers with small molecule SDF format, then imported them into chembio3d ultra 14.0 for energy minimization respectively. The three-dimensional structure of the RRM2 protein was obtained from the PDB (http://www.rcsb.org). AutoDock vina1.1.2 was used to complete the molecular docking between RRM2 protein and TCM monomers. The relevant parameters of RRM2 protein were set to center_x = -4.715, center_y = -3.6 and center_Z = 15.668, the size of the grid box was set to 50 × 50 × 50 (the spacing of each grid point is 0.375 Å), and the other parameters were the default settings. Finally, analysis of the interaction mode of the docking results was performed by PyMol 2.3.0 and ligplot V2.1.

RESULTS

RRM2 was identified as the tumor therapeutic target
In the GEPIA database, we found 31 types of tumor tissues with RRM2 differential expression and their paired normal samples. The findings revealed that, except for LAML, the mRNA expression of RRM2 in 30 types of tumor tissues was considerably higher than that in normal tissues (Figure 1). The investigation of the overall survival rate of 33 types of tumor patients revealed that the RRM2 gene expression of 23 types was negatively correlated with the overall survival rate (Figure 2), while it was positively correlated in 10 types (Figure 3). Among them, the reason for the few positive correlation results observed may be other issues exist that affect the overall survival rate.

Seven TCM monomers with inhibitory effect on RRM2 in tumors were screened
Through the literature search in the PubMed database and CNKI database, we found seven TCM monomers that may be used as RRM2 inhibitors in tumors (Table 2). They all will be described in subsequent sections separately.

Berberine: Berberine is a quaternary ammonium alkaloid extracted from medicinal plants such as Coptis chinensis, Berberis aristata, Hydrastis canadensis, and Coptis japonica[12]. Berberine and its derivatives have been identified to have pharmacological properties against multiple diseases, including digestive diseases, metabolic diseases, cardiovascular diseases, and neurological diseases[13]. Recent studies have discovered that berberine can also inhibit the invasion and metastasis of many kinds of tumors, such as oral squamous cell carcinoma, lung cancer, liver cancer, glioblastoma, breast cancer, and so on[12]. Through binding to P53, NF-κB, matrix metalloproteinase (MMP), Bcl-2, and receptors e.g. estrogen receptor, berberine could promote the cell cycle arrest and death of tumor cell lines, and induce the expression of pro-apoptotic factors[14-16]. In addition, some other information indicates that RRM2 may also be a potential target of berberine in the treatment of tumors. A bioinformatics analysis showed that RRM2 is the hub-gene for berberine to act on breast cancer[17]. After berberine treatment in vitro, the expression level of the RRM2 gene and protein in non-small cell lung cancer cell lines (A549, H1299, and H1975) was significantly reduced[18].

Ursolic acid: Ursolic acid, a natural pentacyclic triterpene compound, is widely found in fruits and vegetables. It has been demonstrated to have multiple biological functions, including anti-inflammatory, antioxidant, anti-apoptotic, and anti-allergic activities[19]. At present, ursolic acid has also been reported to have anti-tumor pharmacological properties, acting as an active therapeutic agent for several malignancies such as breast cancer, colon cancer, pancreatic cancer, and liver cancer[20]. By regulating a variety of enzymes (ATPase, GST, COX-2), transcription factors (AP-1, NF-κB, STAT-3), growth factors (EGF, PDGF, HGF), receptors (EGFR, ER-α, HER-2, EAR), as well as inflammatory factors (MAP-K, PKA, PTK, IL-6, IL-1, IL-8, MIP), it could inhibit tumor proliferation, metastasis, and angiogenesis[21,22]. Recently, a network pharmacology analysis detected that RRM2 may also the
Table 1 Tumor abbreviations

| Abbreviation | Full name                                      | Abbreviation | Full name                                      | Abbreviation | Full name                                      |
|--------------|------------------------------------------------|--------------|------------------------------------------------|--------------|------------------------------------------------|
| ACC          | Adrenocortical carcinoma                       | BLCA         | Bladder Urothelial Carcinoma                   | BRCA         | Breast invasive carcinoma                      |
| CESC         | Cervical squamous cell carcinoma and endocervical adenocarcinoma | CHOL         | Cholangio carcinoma                            | COAD         | Colon adenocarcinoma                           |
| DLBC         | Lymphoid Neoplasm Diffuse Large B-cell Lymphoma | ISCA         | Esophageal carcinoma                            | GBM          | Glioblastoma multiforme                        |
| HNSC         | Head and Neck squamous cell carcinoma          | KICH         | Kidney Chromophobe                              | KIRC         | Kidney renal clear cell carcinoma              |
| KIRP         | Kidney renal papillary cell carcinoma          | LAML         | Acute Myeloid Leukemia                         | LGG          | Brain Lower Grade Glioma                       |
| LIHC         | Liver hepatocellular carcinoma                 | LUAD         | Lung adenocarcinoma                             | LUSC         | Lung squamous cell carcinoma                   |
| MESO         | Mesothelioma                                   | OV           | Ovarian serous cystadenocarcinoma               | PAAD         | Pancreatic adenocarcinoma                      |
| PCPG         | Pheochromocytoma and Paraganglioma             | PRAD         | Prostate adenocarcinoma                         | READ         | Rectum adenocarcinoma                          |
| SARC         | Sarcoma                                        | SKCM         | Skin Cutaneous Melanoma                        | STAD         | Stomach adenocarcinoma                         |
| UCEC         | Uterine Corpus Endometrial Carcinoma           | UCS          | Uterine Carcinosarcoma                          | UVM          | Uveal Melanoma                                 |
| TGCT         | Testicular Germ Cell Tumors                    | THCA         | Thyroid carcinoma                              | THYM         | Thymoma                                        |

Table 2 The traditional Chinese medicine monomers confirmed or predicted having ribonucleotide reductase M2 inhibition in tumors

| Name                | In vivo study | In vitro study | Bioinformatics analysis                      |
|---------------------|---------------|----------------|---------------------------------------------|
| Berberine           | -             | Non-small cell lung cancer | Breast cancer |
| Ursolic acid        | -             | -              | Hepatoma, Colon cancer                      |
| Gambogic acid       | Pancreatic cancer | Pancreatic cancer | -                                           |
| Osalmide            | Endometrial carcinoma | Endometrial carcinoma | -                                           |
| Quercetin           | -             | -              | Hepatoma, Colon cancer                      |
| Daphnetin           | -             | -              | -                                           |
| Gambogic acid       | Pancreatic cancer | Pancreatic cancer | -                                           |
| Cinobufagin         | Endometrial carcinoma | Endometrial carcinoma | -                                           |
| G9a                 | -             | -              | -                                           |
| Multiple myeloma    | -             | -              | -                                           |

potential target of ursolic acid in tumors[23], but still needs to be further confirmed in clinical and experimental studies.

Gambogic acid: Gambogic acid, a kind of caged xanthone extracted from dry resin secreted by Garcinia hanburyi tree, has the functions of promoting blood circulation, anti-tumor, detoxification, and hemostasis[24]. According to numerous studies, multiple carcinomas, including breast cancer, lung cancer, liver cancer, colon cancer, and pancreatic cancer, were inhibited by gambogic acid[25]. Through the combination of several major targets such as VEGF, Bcl-2, MDM2, MMP-9, MMP-2, EGFR, and P53, gambogic acid promotes tumor cell apoptosis, autophagy, and arrests cell cycle, thereby inhibiting tumor invasion, metastasis, and angiogenesis[26]. An investigation in pancreatic cancer demonstrated that following treatment with gambogic acid in vivo and in vitro, the expression of RRM2 protein and mRNA was significantly decreased[6], suggesting that RRM2 may also be the target of gambogic acid in tumor treatment.

Cinobufagin: Bufadienolide cinobufagin, which is extracted from the Asiatic toad Bufo gargarizans, has analgesic, detoxifying, and detumescent properties[27]. Some investigations conducted recently have revealed that it has potent anti-tumor effects as well. In non-small cell lung cancer, cinobufagin could suppress proliferation, migration, and invasion of cancer cells by inhibiting the expression of G9a[27]. By interfering with the cell cycle, cinobufagin also inhibits the survival of cancer cells and promotes apoptosis[28]. Moreover, many other anti-tumor pathways are involved, such as the Notch signaling
The median ribonucleotide reductase M2 gene expression profile across all tumor samples and paired normal tissues (bar plot). The specific results are shown in Figure 1. The screened TCM monomers have a good binding capacity with RRM2 protein, and the results showed that they all had a strong binding capacity. The specific results are presented in the following text.

**Quercetin:** Quercetin, a flavonol compound widely existing in many plants, has been reported to have multiple pharmacological effects on preventing osteoporosis, cardiovascular disease, aging, and tumors. In terms of anti-tumor properties, the main mechanisms are to regulate the viability, apoptosis, and autophagy of tumor cells through PI3K/Akt/mTOR, Wnt/β-Catenin, and MAPK/ERK1/2 pathways, and then exhibit inhibitory activities against a variety of tumors, such as colon cancer (Caco-2 cell line), lung cancer (NCI-H446, A549 cell line), and gastric cancer (MGC-803, SGC-7901 cell line). A comprehensive analysis based on differential genes and drug targets found that quercetin was closely related to RRM2.[33]. After treatment with quercetin, the activity of Leishmania donovani was inhibited by targeting RR[34]. Therefore, we speculate that the anti-tumor effect of quercetin may be partially attributed to the inhibition of RRM2.

**Daphnetin:** Daphnetin is a coumarin derivative with rich pharmacological activity, extracted from Daphne odora. It is often used in the treatment and research of neurological diseases, malaria, parasites, and arthritis[39]. Currently, some studies suggest that daphnetin also has an inhibitory effect on tumor growth, with the mechanisms of action including downregulating Cyclin D1 expression in breast cancer (MCF-7 cell line), inducing G2/M and S phase arrest in hepatoma cells (SMMC-7721 cell line), suppressing the Akt/Neat1 signaling pathway in lung adenocarcinoma (A549 cell line), and inhibiting the AMPK/Akt/mTOR pathway in ovarian cancer (A2780 cell line).[40]. In addition, a study on malaria found that daphnetin could also inhibit the expression and activity of RR by binding to the iron-containing group (RRM2).[41]. However, as an indispensable key enzyme for tumor growth, whether daphnetin can inhibit RRM2 in human tumor cells needs further research to confirm.

**Osalmid:** In clinical practice, osalmid has been used to treat biliary tract inflammation, cholecystitis, and post cholecystectomy syndrome. By decreasing RRM2 activity and activating P53, it was found that osalmid also inhibits the progression of human hepatocellular carcinoma.[42]. The expression of RRM2 in esophageal cancer was similarly inhibited by osalmid. In addition to promoting apoptosis, blocking cell cycle and DNA damage, and inhibiting the proliferation and migration of tumor cells, the radiosensitivity was enhanced.[43]. Due to their powerful anti-tumor activities, osalmid and its derivatives have been used in numerous investigations as new RRM2 inhibitors[44-46].

**The screened TCM monomers have a good binding capacity with RRM2 protein**

Molecular docking presented interaction between the aforementioned seven TCM monomers and RRM2 protein, and the results showed that they all had a strong binding capacity. The specific results are...
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[Graphs and images showing survival analysis for various cancer types]
Figure 2 The twenty-three types of tumors with a negative correlation between ribonucleotide reductase M2 gene expression and overall survival rate. ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; UVM: Uveal Melanoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; UCEC: Uterine Corpus Endometrial Carcinoma.

Figure 3 The ten types of tumors with a positive correlation between ribonucleotide reductase M2 gene expression and overall survival rate. BRCA: Breast invasive carcinoma; CHOL: Cholangio carcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; LUSC: Lung squamous cell carcinoma; OV: Ovarian serous cystadenocarcinoma; READ: Rectum adenocarcinoma; STAD: Stomach adenocarcinoma; THYM: Thymoma; UCS: Uterine Carcinosarcoma.
described in detail in the following sections (Table 3).

Berberine bonded to the RRM2 protein with a binding energy of -7.3 kcal/mol, mostly made up of one hydrogen bond and eight hydrophobic bonds (Figure 4A). The hydrogen bond was mainly localized at Ser263(A) of RRM2, with a length of 3.73 Å, and the hydrophobic sites were situated at Glu260(A), Arg264(A), Tyr323(A), Arg330(A), Gly233(A), Val327(A), Ser263(A) and Gly267(A) of RRM2.

Ursolic acid and RRM2 protein had binding energy of -8.6 kcal/mol (Figure 4B). There was just hydrophobic force between them. Arg264(A), Gly267(A), Cys270(A), Gly233(A), Arg330(A), Val327(A), Ser263(A), Phe244(A), Phe349(A), and Met350(A) of RRM2 were the primary hydrophobic action sites.

Gamboic acid and RRM2 protein bonded with a -8.6 kcal/mol binding energy (Figure 4C). Their interaction was achieved through the formation of hydrogen bonds and hydrophobic forces. The hydrogen bonds in RRM2 were at positions Arg330(A) and Tyr323(A), with lengths of 3.24 Å and 2.74 Å, respectively. The hydrophobic action sites in RRM2 were found at Gly267(A), Leu268(A), Ser100(A), Lys96(A), Arg264(A), Met350(A), and Ser263(A).

The binding energy between cinobufagin and RRM2 protein was -7.6 kcal/mol (Figure 4D). They interacted with each other through the formation of hydrogen bonds and hydrophobic force. The hydrogen bond lengths were 3.88 Å and 2.82 Å, respectively, which were located at Asp271(A) and Arg330(A) of RRM2. The hydrophobic effect was generated on Glu334(A), Leu331(A), Cys270(A), Gly267(A), Glu266(A), Ser263(A), Phe244(A), and Met350(A) of RRM2 and cinobufagin.

Quercetin and RRM2 protein had binding energy of -7.4 kcal/mol (Figure 5A). Quercetin mainly forms three hydrogen bonds and nine hydrophobic forces with RRM2. The hydrogen bond lengths were 3.16 Å, 3.05 Å, and 2.77 Å, respectively, which were mainly formed in Arg330(A) and Tyr323(A) of RRM2. The hydrophobic sites were found in the following positions in RRM2: Met350(A), Arg264(A), Glu260(A), Phe244(A), Ser263(A), Glu232(A), Gly233(A), Phe240(A) and Val327(A).

The binding energy between daphnetin and RRM2 protein was -6.7 kcal/mol (Figure 5B). Tyr323 (A) and Arg330 (A) of RRM2 made four hydrogen bonds with daphnetin, whereas Val327(A), Ser263(A), Phe240(A), Met350(A), Gly267(A), Gly233(A), Cys270(A) of RRM2 formed seven hydrophobic forces with daphnetin. Whose hydrogen bonds had lengths of 2.87 Å, 3.19 Å, 2.80 Å, and 3.24 Å, respectively.

Osalmide and RRM2 protein had a -6.8 kcal/mol binding energy (Figure 5C). They only interacted hydrophobically, and their hydrophobic interaction sites were found in Phe244(A), Arg264(A), Tyr323(A), Phe240(A), Ser237(A), Met350(A), Gly233(A), and Ser263(A) of RRM2.

**DISCUSSION**

Nowadays, the acknowledged tumor treatment strategies include surgical resection, chemotherapy, and radiotherapy, as well as biotherapy, immunotherapy, and targeted therapy developed in recent decades. Due to some limitations and defects, monotherapy does not seem to be able to fully achieve the ideal effect[47]. Therefore, combination therapy and adjuvant therapy are often required. As a natural medicine, some active ingredients of TCM have been proven to have excellent anti-tumor activity. TCM can not only inhibit the proliferation of tumor cells through multiple targets, improve the cancer microenvironment, and strengthen the function of anti-tumor immunity, but also enhance the efficacy of chemotherapy, radiotherapy, targeted therapy, and immunotherapy, and reduce the damage caused by these therapies, to prolong the survival time of tumor patients and improve the quality of life to a certain extent[48]. Because of their advantages of broad spectrum, high efficacy, low toxicity, and strong specificity, TCMs and extracts are widely used as adjuvant therapy for tumors in clinics[49]. Paclitaxel, vinblastine, and hydroxycamptothecin are three examples of commonly used clinical chemotherapeutic medicines[50-52]. Compared with traditional synthetic medications, the anti-tumor mechanisms of TCMs are more complex and extensive. They involve multiple signaling pathways and biological targets related to cancer. Despite the long history of TCM study, part of the mechanism of action and molecular targets are not completely clear[53]. TCM monomers, as the active compound of TCM, including their functions still need to be further explored and studied.

Deoxyribonucleotide triphosphate (dNTP), the building block for DNA synthesis, is in high demand in tumors. As the key enzyme of DNA synthesis, RR not only participates in DNA synthesis and repair via producing dNTP but is also involved in cell cycle regulation[5, 54]. RRM2 is an important subunit of RR, which also play a regulatory role in multiple biological processes, including the survival, proliferation, apoptosis, and chemoresistance of various cancer cells[7]. According to GEPIA database analysis, we found that RRM2 is highly expressed in more than 30 types of tumor tissues, and negatively correlated with the overall survival rate of patients with the majority of tumor types. A study in prostate cancer has found that RRM2 is a driver of aggressive subtypes, and elevated RRM2 contributes to tumor cell immune escape[55]. The overexpression of RRM2 in breast cancer cells activated NF-κB and MMP-9 to alter the tumor microenvironment, thereby enhancing the migratory abilities of tumor cells[56]. Increased RRM2 expression is also associated with tamoxifen resistance, inhibition of RRM2 not only reduced migration and invasion characteristics of cancer cells in vitro but also reversed tamoxifen resistance of breast cancer cells, which may be mediated by NF-κB, HIF-1α, and...
Table 3 The binding energy and binding sites of the selected traditional Chinese medicine monomers with ribonucleotide reductase M2

| Names          | Binding energy | Hydrogen bond site          | Hydrophobic bond site                        |
|----------------|----------------|-----------------------------|----------------------------------------------|
| Berberine      | -7.3 kcal/mol  | Ser263 (A)                  | Glu260(A), Arg264(A), Tyr323(A), Arg330(A), Gly233(A), Val327(A), Ser237(A), and Gly267(A) |
| Ursolic acid   | -8.6 kcal/mol  | -                           | Arg264(A), Gly267(A), Cys270(A), Gly233(A), Arg330(A), Val327(A), Ser263(A), Phe244(A), Phe549(A), and Met350(A) |
| Gambogic acid  | -8.6 kcal/mol  | Arg330(A) and Tyr323(A)     | Gly267(A), Leu268(A), Ser100(A), Lys96(A), Arg264(A), Met350(A), and Ser263(A) |
| Cinobufagin    | -7.6 kcal/mol  | Asp271 (A) and Arg330 (A)   | Glu334 (A), Leu331 (A), Cys270 (A), Gly267 (A), Glu266 (A), Ser263 (A), Phe244 (A), and Met350 (A) |
| Quercetin      | -7.4 kcal/mol  | Arg330 (A) and Tyr323 (A)   | Met350 (A), Arg264 (A), Gly260 (A), Phe244 (A), Ser263 (A), Glu232 (A), Gly233 (A), Phe240 (A) and Val327 (A) |
| Daphnetin      | -6.7 kcal/mol  | Tyr323 (A) and Arg330 (A)   | Val327 (A), Ser263 (A), Phe240 (A), Met350 (A), Gly267 (A), Gly233 (A), and Cys270 (A) |
| Osalmide       | -6.8 kcal/mol  | -                           | Phe244 (A), Arg264 (A), Tyr323 (A), Phe240 (A), Ser237 (A), Met350 (A), Gly233 (A), and Ser263 (A) |

Figure 4 Berberine/ursolic acid/gambogic acid/cinobufagin and RRM2 protein have binding energy. A: The molecular docking diagram of berberine with ribonucleotide reductase M2 (RRM2) protein; B: The molecular docking diagram of ursolic acid with RRM2 protein; C: The molecular docking diagram of gambogic acid with RRM2 protein; D: The molecular docking diagram of cinobufagin with RRM2 protein.

MAPK/JNK pathways[57]. GW8510 acts as an RRM2 inhibitor, improving acquired tamoxifen resistance in breast cancer cells by autophagy induction, a similar effect was seen in lung squamous cell carcinoma cells[58,59]. Besides, knockdown of RRM2 enhanced the drug sensitivity of chronic myeloid leukemia to imatinib treatment by activating the Bcl-2/caspase apoptosis pathway and inhibiting the Akt cell signaling pathway[60]. These results indicate that RRM2 is an independent predictor of poor prognosis in a variety of tumors and could be a good target for tumor therapy.

RRM2 has two important drug binding targets: tyrosine free radical and divalent iron radical, most of the currently developed RRM2 inhibitors act on these two targets[61]. Hydroxyurea is a common anti-tumor chemotherapy drug as well as an RRM2 inhibitor, which can inhibit RRM2 activity by scavenging tyrosine free radicals, and then inhibit DNA synthesis[62]. Gallium, an iron analog, has chemical characteristics similar to iron. Though interacting with iron-binding protein, gallium interferes with cellular iron uptake and damages iron homeostasis in cells, resulting in the inhibition of RRM2 function[63]. Triapine also inhibits RRM2 activity by forming iron chelates with iron groups[64]. However, some
RRM2 inhibitors may lead to different degrees of side effects such as blood and lymphatic system metabolic disorders, liver and kidney dysfunction, gastrointestinal reactions, and reproductive toxicity [65,66]. Therefore, it is urgent to develop or find new RRM2 inhibitors that are safer, more effective, and more specific.

Through literature mining, we retrieved seven TCM monomers with an inhibitory effect on RRM2 in tumors. They all have good binding capacities with RRM2, according to molecular docking analysis, with binding energies ranging from -8.6 to -6.8 kcal/mol. The hydrogen bonds and/or hydrophobic forces are the main contributors to these binding energies, their major active sites are Arg330, Tyr323, Ser263, and Met350 of RRM2. Among them, Arg330 is the site where the most hydrogen bonds are formed between TCM monomer and RRM2, followed by Tyr323. The locations with the highest frequency of hydrophobic action are Ser263 and Met350, the next two are Gly267 and Arg264. These findings imply that Arg330, Tyr323, Ser263, and Met350 may be important binding sites of RRM2 inhibitors with RRM2, which will provide some thoughts for the development of new anti-tumor drugs with RRM2 inhibition based on these sites.

CONCLUSION

RRM2 is a crucial tumor therapeutic target. It is highly expressed in almost all tumors and negatively correlated with the overall survival rate of patients with the majority of tumor types. The seven screened TCM monomers have a good binding capacity to RRM2, and their binding sites are mainly concentrated in Arg330, Tyr323, Ser263, and Met350 of RRM2. This will provide theoretical support and a point for the development of anti-tumor medications with RRM2 inhibition based on these binding sites. Meanwhile, natural drugs with abundant structures are an important source for the development of anti-tumor drugs, it is anticipated that more effective RRM2 inhibitors will be developed through in-depth research.

ARTICLE HIGHLIGHTS

Research background

The tumor is a major contributor to endangering human health, traditional Chinese medicine (TCM) monomer is an important source of anti-tumor drugs. Ribonucleotide reductase (RR) is a key enzyme in tumor proliferation, especially its subunit-RRM2. Screening and analysis of TCM monomers with RRM2 inhibitors may lead to different degrees of side effects such as blood and lymphatic system metabolic disorders, liver and kidney dysfunction, gastrointestinal reactions, and reproductive toxicity [65,66]. Therefore, it is urgent to develop or find new RRM2 inhibitors that are safer, more effective, and more specific.

Figure 5 Quercetin/daphnetin/osalmide and ribonucleotide reductase M2 protein have binding energy. A: The molecular docking diagram of quercetin with ribonucleotide reductase M2 (RRM2) protein; B: The molecular docking diagram of daphnetin with RRM2 protein; C: The molecular docking diagram of osalmide with RRM2 protein.
inhibition can provide a reference for further anti-tumor drug development.

**Research motivation**
To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2, and provide some thoughts for the development of anti-tumor drugs with RRM2 inhibition in the future.

**Research objectives**
To clarify the relationship between RRM2 and malignant tumors. To clarify the relationship between RRM2 and the prognosis of tumor patients. To screen and analyze potential anti-tumor TCM monomers with a good binding capacity to RRM2, and provide some thoughts for the development of anti-tumor drugs with RRM2 inhibition in the future.

**Research methods**
The GEPIA database was used to analyze the level of RRM2 gene expression in normal and tumor tissues as well as RRM2’s effect on the overall survival rate of tumor patients. TCM monomers that potentially act on RRM2 were screened via literature mining. Using AutoDock software, the screened monomers were docked with the RRM2 protein.

**Research results**
The expression of RRM2 mRNA in multiple tumor tissues was significantly higher than that in normal tissues, and RRM2 was negatively correlated with the overall survival rate of patients with the majority of tumor types. Berberine, ursolic acid, gambogic acid, cinobufagin, quercetin, daphnetin, and osalmide have inhibitory effects on RRM2. The screened TCM monomers had a strong binding capacity with RRM2 protein.

**Research conclusions**
RRM2 is an important tumor therapeutic target. The screened TCM monomers have a good binding ability with the RRM2.

**Research perspectives**
Their main binding sites could provide new thoughts for the development of anti-tumor drugs with RRM2 inhibition.

**FOOTNOTES**

**Author contributions:** Qin YY wrote the manuscript, designed the study, and acquired data; Feng S acquired, analyzed, and interpreted the data; Zhang XD supervised, reviewed, and edited the manuscript; Peng B designed and coordinated the study, collected funds; all authors approved the final draft.

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**Country/Territory of origin:** China

**ORCID number:** Ya-Ya Qin 0000-0002-2663-5819; Song Feng 0000-0002-3920-9245; Xiao-Dong Zhang 0000-0001-9858-8647; Bin Peng 0000-0002-6947-2570.

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