

Advances of wogonin, an extract from *Scutellaria baicalensis*, for the treatment of multiple tumors

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Abstract: As the major bioactive compound of *Scutellaria baicalensis* that has been approved to be effective as an anti-inflammatory and antiviral inhibitor in cardiovascular diseases, wogonin (WG) showed potent and promising antitumor effects both in vitro and in vivo. It has been proved that WG has the ability to inhibit the growth of tumor cells, induce apoptosis, and suppress angiogenesis. The molecular mechanisms involve reactive oxygen species, Ca²⁺, NF-κB, tumor necrosis factor-related apoptosis-inducing ligand, and tumor necrosis factor-alpha. Furthermore, the synergistic effect of WG with 5-fluorouracil, etoposide, and adriamycin to enhance chemotherapy and reverse drug resistance has also been confirmed. In this review, we summarize the advances in recent years on the antitumor effect of WG on multiple tumors; in addition, we also present information regarding the synergistic and chemosensitizing effects of WG with other drugs to illustrate its potential use in the clinic.

Keywords: antitumor effect, drug resistance, mechanisms, synergistic effect

Introduction

During the last 20 years, wogonin (WG; 5,7-dihydroxy-8-methoxyflavone) was identified as a potent apoptosis inducer of cancer cells, showing its maximal efficacy with minor side effects.¹ Furthermore, pharmacokinetic studies in rats make the use of WG in the clinic possible.² Fortunately, it has been approved for Phase I clinical trial in the People's Republic of China (December 2014, approved by the China Food and Drug Administration).

WG is extracted from *Scutellaria baicalensis* Georgi (Huang Qin), a perennial Labiate, and its molecular formula is C₁₆H₁₂O₅ (Figure 1). Several studies have shown its inhibitory activity on the viability and the growth of tumor cells.³ Various investigations have also demonstrated that WG exerts its antitumor effects via regulation of multiple molecular pathways. The key molecular pathways of its antitumor effects include reactive oxygen species (ROS), Ca²⁺, NF-κB, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor-alpha,^{4–8} which participate in both intrinsic mitochondria-mediated and extrinsic receptor-mediated pathways.⁹ In addition to its activation of Bax/Bak protein and caspase-8/caspase-9/caspase-3, WG plays an important role to inhibit lipopolysaccharide-induced or hydrogen peroxide (H₂O₂)-induced tumor angiogenesis through PI3K/AKT/NF-κB pathway.^{10–12} In addition, the ability of WG to inhibit tumor angiogenesis by decreasing the expression of hypoxia-inducible factor-1α protein was also observed.¹³

The current review is not only limited to the induction of apoptosis of tumor cells by WG but also dedicated to its synergistic effects with other chemotherapeutic

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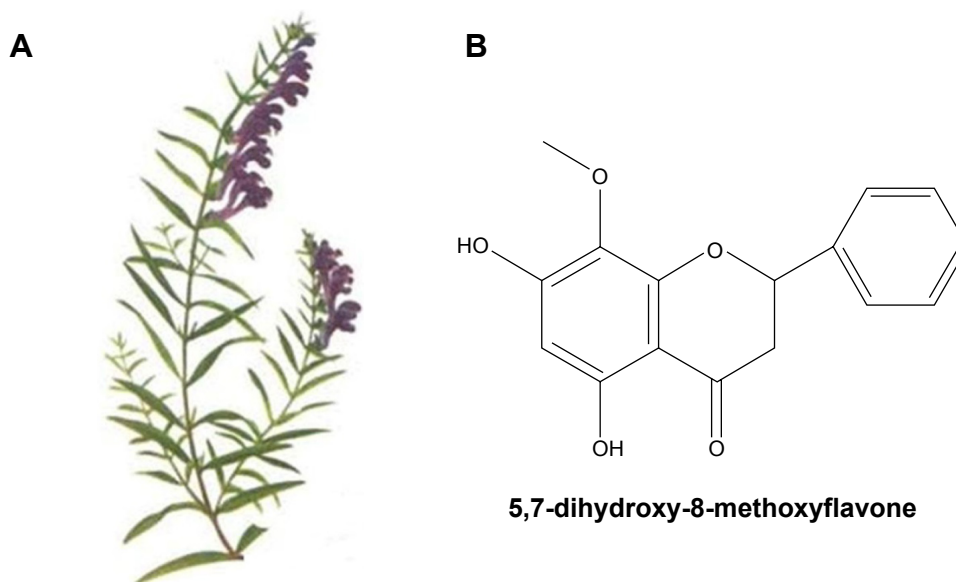


Figure 1 *Scutellaria baicalensis* Georgi (Huang Qin) and WG.
Notes: (A) The plant of Huang Qin. (B) The chemical structure of WG.
Abbreviation: WG, wogonin.

drugs and its ability to reverse drug resistance of tumors (chemosensitizer), aiming to summarize its new developments for its future clinical use.

Anticancer effects on multiple tumors in vitro and in vivo Hematologic malignancies

Leukemia, multiple myeloma, and lymphoma are the three main kinds of hematologic malignancies with the highest mortality rate. Since the study of Huang et al¹⁴ in 2010 where they investigated the effects of 29 compounds from the extracts of *S. baicalensis* on leukemia cell lines, WG's ability to induce apoptosis in tumor cells has been considered. At the same time, the extracts from *Scutellaria pinnatifida*, such as dichloromethane, methyl alcohol, ethyl acetate, and *n*-butyl alcohol, were tested on two different leukemia cell lines and a normal cell line, by Boozari et al.¹⁵ Among them, the extract of dichloromethane showed the highest cytotoxic effects and the possibility to regulate the expression of the proteins, which were related to apoptosis, and the cell cycle was blocked at the G1 phase. Furthermore, the study also showed that WG was the main active component in the dichloromethane extract of *S. pinnatifida*, indicating its role as a cytotoxic drug.¹⁵ On the other hand, Ozmen et al¹⁶ demonstrated that WG could induce genotoxic stress at the concentration of 132 µg/mL on HL-60 cells after treatment for 48 hours, leading to the appearance of substantial phosphorylation of the core histone H2AX (gamma-H2AX)

followed by the activation of caspase-3 and signature-type cleavage of PARP, which caused apoptosis in >55% of HL-60 cells.

Moreover, the anticancer effect of WG was investigated in the mouse model of leukemia. A study in vivo showed that WG could increase the survival rate of leukemic mice by increasing the percentage of CD3 (T cells) and CD19 (B cells) and reducing the percentage of Mac-3 (macrophages) and CD11b (monocytes) cell surface markers.¹⁷ In 2014, peripheral blood leukocytes obtained from patients with acute lymphoblastic leukemia were used to identify the antitumor potential of WG. Interestingly, the results confirmed that WG is not only capable of inducing the apoptosis of acute lymphoblastic leukemia cells but also has good selectivity for tumor cells.¹⁸

Research on the possible effects of WG for the treatment of multiple myeloma and lymphoma have been explored as well. The studies both in vitro and in vivo confirmed that WG induced apoptosis of myeloma cells via the intrinsic apoptotic pathway,^{19,20} which made WG a potential therapeutic drug for multiple myeloma. On the other hand, Wang et al investigated the effect of WG on lymphoma cells, and the result showed that WG could induce the apoptosis of B-cell lymphoma. Furthermore, they combined WG with magnetic nanoparticles as a drug delivery system to explore whether it could increase the efficiency of WG-induced apoptosis, which opened another era for the use of Chinese traditional medicines with advanced technologies for drug delivery.²¹

Solid tumors

Solid tumors account for ~90% of all cancers. The recorded death rate in the US was 23% of the total population in 2011. Previously, due to the limited use of effective therapies, solid tumors represent a major cause of death. A decrease in the mortality rate caused by cancers from 2011 to 2015 was recorded, as the molecular mechanisms for tumor development were explored widely; in addition, new drugs were designed and introduced as targeted chemotherapeutic agents.²² The underlying molecular mechanisms by which WG has been demonstrated to exert its effect as antitumor agent are summarized in Table 1.

Digestive carcinomas

Hepatocellular carcinoma (HCC) is a refractory malignancy, which has a high incidence and mortality rate all over the world, especially among Asian populations.²³ Lack of

systemic chemotherapeutic regimens and effective surgical resection results in poor prognosis in most patients. In recent years, natural products have been increasingly recognized as new remedies for enhancing the efficacy and alleviating the adverse effects of tumor therapies. To explore the antitumor effects of WG on HCC, Xu et al evaluated the efficacy of WG on three types of HCC cell lines and tumor cell xenografts as well. The results confirmed the induced-apoptotic effect of WG on HCC and indicated that the resultant cytotoxicity was partially attributed to the unfolded protein response where AKT pathways played an important role in that process. The production of intracellular H₂O₂ and the release of endoplasmic reticulum (ER) Ca²⁺ might be the beginning of this effect.²⁴

Most colorectal cancers (CRC) have high incidence in people from the developed countries rather than those from the developing countries. The incidence and mortality rates

Table 1 Molecular mechanisms through which WG interacts with various types of tumors

Tumor type	Cell lines	Key signaling	References
Leukemia	HL-60	Caspase-3↑, Bcl-2↓, telomerase activity↓	14
		Caspase-3↑, H2AX phosphorylation, cleavage of PARP	15, 16
Multiple myeloma	NALM-6	VEGF, cMyc, NF-κB↓	18
		ABCG2 protein↓, Akt1 protein↓	19, 20
HCC	HepG2	Bcl-2↓, Bax protein↑, pro-caspase-3↑	24
		ROS, ER stress	24
CRC	SMMC-7721	Nrf2↓	24
		PI3K/AKT↓, Bax↑, Bcl-2↓, caspase-3↑, p21	24
Breast cancer	HCT116	HIF-1α↓, PI3K/AKT↓	29
		G1 arrest, Wnt/β-catenin↓	30
Glioma	HT-29	NF-κB, Nrf2, AKT	27, 31, 32
		PI3K/AKT↓	11, 36–38
Lung cancer	MCF-7	ERK↑, p38 MAPKs↑, HIF-1α↑	39
		PKCδ↓, ERK phosphorylation, MMP-9↓	40
Cervical cancer	MDA-MB-231	AKT↓, GSK-3β↓, NF-κB↓	47
		G1 arrest, GSK-3β↓, AKT↓	48
Nasopharyngeal carcinoma	F98	PKCα, ERK, NF-κB, MMP-9	49
		ROS, ER stress	50, 51, 53
Osteosarcoma	C6 and U251	AMPK, p53	52
		p53↑, Bax↑	55
Melanoma	GBM8401	ROS	56
		IL-6/STAT3	57
Digestive carcinomas	U87 and U251	COX-2↓, c-Jun↓, AP-1↓	58
		p53↑, Bax↑, Cyclin D1	55
Solid tumors	U87-MG, U343-MG, U373, T98G, and MCF-10A	p53, p21 Cip1	59
		E6↓, E7↓	60
Digestive carcinomas	A549	GSK-3β↓, ΔNp63↓	61
		mTOR/P70S6K, AKT, Raf/ERK	62
Digestive carcinomas	SK-MES-1	ER stress	63
		Extracellular regulated protein kinases and protein kinase B	64
Digestive carcinomas	HeLa		
Digestive carcinomas	HPV-16		
Digestive carcinomas	NPC-TW076/039		
Digestive carcinomas	U-2 OS		
Digestive carcinomas	B60-F10		

Abbreviations: HCC, hepatocellular carcinoma; CRC, colorectal cancer; WG, wogonin; ROS, reactive oxygen species; ER, endoplasmic reticulum; Nrf2, NF-E2-related factor 2; ERK, extracellular signal-regulated kinase.

for the elderly population in the more developed areas were 4.3% and 1.6%, respectively.²³ The exploration of WG effects on CRC was always accompanied by the discoveries of colitis and inflammation-associated colorectal carcinogenesis,^{25,26} in which the key molecules involved were discovered recently to be NF- κ B and NF-E2-related factor 2 (Nrf2).²⁷ A study in 2013 showed that WG had a strong chemosensitizing effect in HCT116 cells under hypoxia. The suggested molecular mechanism might be that WG could downregulate the expression of HIF-1 α , which activated the expression of related target genes through inhibiting PI3K/AKT signaling pathway in vitro and in vivo.²⁸ Meanwhile, He et al also demonstrated that WG could induce cell cycle arrest at the G1 phase in HCT116 cells in a concentration and time-dependent manner by downregulating Wnt/ β -catenin signaling pathway.²⁹ The current reports about the mechanisms of WG-induced apoptosis in HT-29 colon cancer cells include mitochondrial-mediated pathway, AKT inactivation, and p53-dependent manner.^{30,31} Besides HCC and CRC, evidence on the potential of WG to induce the apoptosis in gallbladder carcinoma and pancreatic cancer still need further exploration.³²⁻³⁴

Breast cancer

Because of its poor prognosis, breast cancer caused 15% of tumor-related death in females, ranking as the second major malignancy in the US in 2015.²² Although new chemotherapeutic drugs and target therapeutic preparations have been introduced, the rate of death continues to rise. A study in 2010 showed that baicalin-deprived-fraction, but not the whole extract of *S. baicalensis*, might have potential to inhibit cell growth and induce cell apoptosis of MCF-7 cells through the PI3K/AKT pathway, which played a critical role as an important signaling downstream of epidermal growth factor receptor for breast cancer.³⁵ Since then, much research has focused on the relationship between the PI3K/AKT pathway and MCF-7 breast cancer cell line. However, the limitation was that almost all the results were restricted to the in vitro experiments, whereas studies in vivo and clinical trials were not reported.^{36,37} Besides being a promising inhibitor of tumor angiogenesis, WG was evaluated by Zhao et al¹¹ to investigate its antitumor effect on breast cancer cells. They concluded that WG could inhibit AKT signaling, suppress tumor angiogenesis, and depress tumor growth eventually.

Recent studies also indicated that the activation of extracellular signal-regulated kinase and p38 MAPKs signaling pathways, which could be inhibited by *N*-acetyl cysteine, an ROS scavenger, was correlated with the cell apoptosis in breast cancer cells treated with WG.³⁸

Therefore, it could be concluded that WG effects on breast cancer might be through ROS pathway.³⁹ In addition to the apoptosis of cancer cells, extracellular signal-regulated kinase also participates in the invasion of breast cancer, which could be inhibited by WG, indicating that WG is an inhibitor of tumor invasion as well.⁴⁰

Neuroblastoma and glioma

As a new potential drug for diseases of the nervous system, WG takes effect as an anti-inflammatory, neuroprotective, and tumor growth inhibitor.⁴¹⁻⁴⁴ The former two effects were confirmed to be associated with NF- κ B and MAPK signaling pathway both in primary microglial cell cultures and in rat dorsal root ganglion neurons.^{45,46} Actually, they also interact with each other since NF- κ B and MAPK signaling also played a critical role in tumor inhibition or apoptosis. In 2011, Parajuli et al⁴⁷ were the first to provide an in vivo evidence about the antiglioma activity of WG, demonstrating that the suppressed growth of the tumor was due to the inhibition of AKT and its downstream signaling, including glycogen synthase kinase (GSK-3) and NF- κ B. The inhibition of GSK-3 β has also been recognized as a key change to induce the differentiation of glioma cells treated with WG. Moreover, in 2013, Wang et al⁴⁸ found that WG could induce the differentiation of glioma cells by diminishing the phosphorylation of AKT and decreasing the expression of β -catenin significantly, both of which were dependent on GSK-3 β activation. Meanwhile, Lin et al⁴⁹ used WG in one study, known as NF- κ B inhibitor, to prevent the migration and invasion of glioblastoma, indicating that the anticancer effect of WG included inhibition of tumor metastasis as well. Other studies of WG on glioma focused on the mechanisms of WG-induced apoptosis that include ROS activation and ER stress activation and mitochondrial dysfunction both in vitro and in vivo.⁵⁰⁻⁵³

Lung cancer

Lung cancer accounts for 14% of the newly estimated cases in 2015 and is the leading cause of mortality among all cancers.²² In 2010, Gao et al⁵⁴ for the first time evaluated the inhibitory effect of eight solvent extracts from *S. baicalensis* on a human lung cancer cell line confirming the role of WG as an inhibitor of human lung cancer. In order to figure out the mechanism as to how WG affects lung cancer, Gao et al⁵⁵ continued the exploration on other lung cancer cell lines, which showed that WG also had the ability to induce the apoptosis of tumor cells. Meanwhile, the in vitro studies about the effect of WG on enhancing TRAIL-induced apoptosis in lung cancer cells has been already in progress

as well, as in 2013 and based on the *in vitro* xenografts investigation results, showed that WG significantly enhanced TRAIL-induced suppression of tumor growth that was regulated by the ROS signaling pathway.⁵⁶ Additionally, evidence showed that WG had the ability to depress tumor metastasis by regulating the inflammatory microenvironment,⁵⁷ demonstrating that it is an effective therapeutic drug for tumor migration.⁵⁸

Others

There is also some research about the antitumor effect of WG on cervical cancer, ovarian tumor, nasopharyngeal carcinoma, osteosarcoma, and melanoma. However, most of the investigations were limited to an *in vitro* evaluation, and the data indicated that AKT, GSK-3 β , and ER stress played an important role in the process of apoptosis induced by WG.^{59–64}

Synergistic reactions with other chemotherapeutic drugs

WG is considered as an adjuvant to potentiate the antitumor efficacy of the drugs and reduce their damage to normal tissues for cancers such as leukemia and HCC.^{65,66} The combination of WG with 5-fluorouracil (5-FU), etoposide, and paclitaxel (PTX) has been widely reported for the treatment of hematological and gastric malignancies (Table 2).

Combination of WG and 5-FU

The use of 5-FU for gastrointestinal cancers in the clinic as an antitumor agent, has a long history of more than half of a century. 5-FU prevents tumor growth by abnormal RNA processing and inhibition of DNA synthesis. However, the unaided use of 5-FU in advanced gastrointestinal cancers generally leads to a very low rate of response and most frequently drug resistance. Thus, the ability of WG as a potential antitumor and chemosensitizing drug was tested to enhance the antitumor effect of 5-FU and minimize drug resistance.

Two positive results were reported indicating the synergistic effect of WG and 5-FU both *in vitro* and *in vivo*. The first one concluded that WG mechanism was due to the inhibition of NF- κ B,⁶⁷ while the other study found that WG enhanced the effect of 5-FU cytotoxicity in HCC through the PI3K/AKT signaling pathway.⁶⁸

Potential of the antitumor effect of etoposide and amelioration of its adverse effects

Etoposide, an antitumor agent for specific cell cycle arrest, is targeted for DNA topoisomerase-II enzyme. It forms a ternary complex with DNA and the topoisomerase II enzyme, preventing the religation of the DNA strands, causing DNA strands to break. Because of its DNA damage effect, normal cells are usually killed during the process of clearing tumor cells, which causes severe myelosuppression. The low toxicity of WG was indicated by the fact that it did not affect the viability of normal T cells and usually acted as an antiapoptotic agent for thymocytes.⁶⁹ Enomoto et al cultured various tumor cells with normal T cells from mice thymus and bone marrow treated with etoposide alone, WG alone, or etoposide combined with WG. The results showed that the cells treated by the combination group had a higher apoptotic rate than both untreated cells and single drug (etoposide or WG) treated cells. However, compared with the group which was treated with etoposide alone, the apoptosis rate of normal T cells of the combination group was much lower. Further study showed that WG inhibited the excretion of calcein, a substrate for P-glycoprotein (P-gp) in the tumor cells, and decreased the excretion of etoposide; thus, it increased the intracellular content of etoposide.⁶⁹ In another study, the attenuating effect of WG on etoposide-induced oxidative DNA damage of normal cells was also investigated in mouse bone marrow cells using oral administration of WG before etoposide injection, which was correlated with the downregulation of OGG1 repair gene and changes in oxidative DNA stress.⁷⁰

Table 2 Common drugs that have synergistic effect with WG and their effects

Name of drug	Tumor type	Effects	In vitro	In vivo
5-FU	Gastrointestinal cancers	Inhibiting the expression of NF- κ B Enhancing the cytotoxicity to HCC, which expressed high COX-2 by PI3K/AKT	√	√
Etoposide	Leukemia and lung cancer	Decreasing the etoposide-induced oxidative DNA damage and apoptosis of other hemocytes	√	
PTX	Gastrointestinal cancers	IC ₅₀ of the combination has been calculated for four gastric cancer cell lines, but no further research was conducted on its mechanisms	√	√

Note: √ means that the relevant studies have been done already.

Abbreviations: WG, wogonin; 5-FU, 5-fluorouracil; HCC, hepatocellular carcinoma; PTX, paclitaxel.

Synergistic effect of WG and PTX

PTX is widely used in antigastric cancers and breast cancers combined with other chemotherapeutic agents such as cisplatin and adriamycin. However, the combinations often bring about severe side effects. The study of Wang et al demonstrated the low IC_{50} and high apoptotic rate of WG and PTX on four gastric cancer cell lines. It was therefore concluded that the combination of WG and PTX had a synergistic inhibitory effect on tumor growth in vitro; a further study also affirmed the result in vivo.⁷¹

Development of WG–Lip complex with other chemotherapeutic drugs

In addition to mixing free plain WG physically with chemotherapeutic drugs to induce antitumor effects, Tian et al connected free WG with liposomes (Lip) to produce WG–Lip complex and then modified the complex by glycyrrhetic acid (GA) in order to get the final product, namely, GA-modified WG Lip (GA–WG–Lip). GA–WG–Lip showed a great rate of uptake and had an IC_{50} value 1.46 times higher than that of WG–Lip. Other advantages of the GA-modified WG Lip included rapidly accumulating in the liver and displaying a better tumor inhibitory effect than that of the unmodified Lip.⁷² Therefore, the future of WG combination with other drugs will not be limited to simple mixing, but the introduction of pharmaceutically modified formulation of WG will predominate the future explorations to achieve better responses and to overcome free WG administration problems.

Chemosensitizing effect

As a major chemotherapeutic obstacle, multidrug resistance (MDR) is currently rendering many available chemotherapeutic drugs ineffective for treating tumors. Researchers found that the inhibition of MDR proteins by WG could improve the intracellular effective drug level and potentiate their chemotherapeutic effects.⁷³ Imatinib is a BCR-ABL kinase inhibitor that is widely used in the clinic for chronic myelogenous leukemia. However, resistance to imatinib leads to a high rate of treatment failure. The study of Yang et al⁷⁴ indicated that WG could inhibit the growth of K562r, one of the MDR cell lines of chronic myelogenous leukemia, and arrest cell cycle at the G0/G1 phase. Besides, the adriamycin-resistant K562 cells (K562/A02) were also used to test the chemosensitizing effect of WG, whose mechanism was discovered to be associated with downregulation of MDR protein 1 expression by inhibiting Nrf2/ARE signaling pathway eventually (Figure 2).⁷⁵ Moreover, WG could also reverse adriamycin resistance of breast cancer cells MCF7/DOX by regulating the expression of P-gp.⁷⁶ Commonly, P-gp has been reported to develop not only the resistance of adriamycin-treated cells but also etoposide-induced apoptosis, which was also a target of WG to chemosensitize in many tumor cells.^{21,77,78}

The effect of sensitizing other chemotherapeutic drugs with WG was also explored in lung cancer, ovarian cancer, and colon cancer which are resistant to traditional chemotherapeutic drugs, for example, platinum. Meanwhile, in addition to the chemosensitizing effect, WG could also enhance the antitumor effect of chemotherapeutic drugs under the

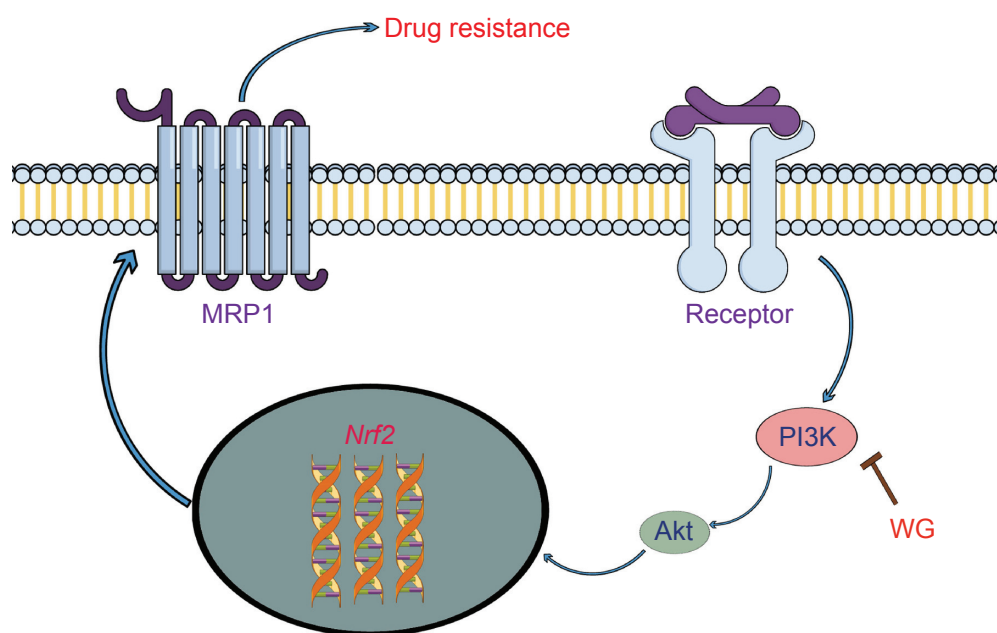


Figure 2 The chemosensitizing of WG by Nrf2-mediated pathway.

Note: WG downregulates the expression of PI3K/Akt to reduce the transcription of Nrf2 mRNA and results in inhibition of MRP1.

Abbreviations: WG, wogonin; Nrf2, NF-E2-related factor 2; MRP1, multidrug resistance protein 1.

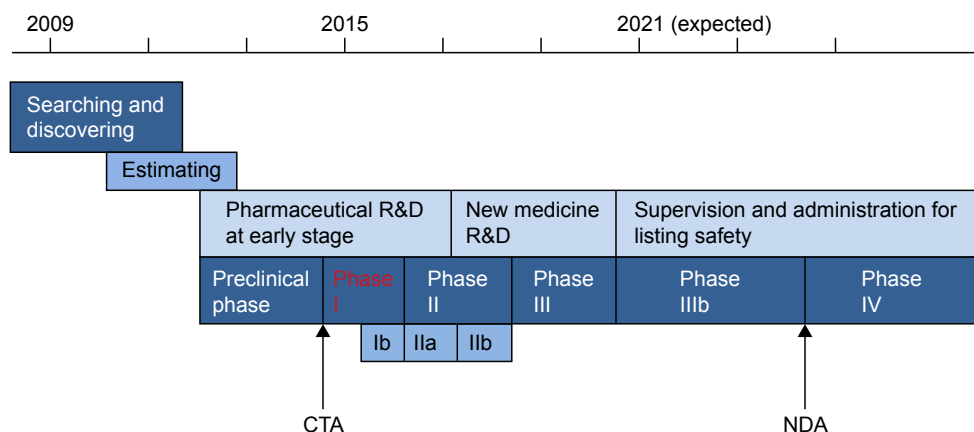


Figure 3 The procedures for WG to be a clinically approved drug.

Note: The red words of Phase I indicate the place where we are currently.

Abbreviations: WG, wogonin; R&D, research and development; CTA, clinical trial admission; NDA, new drug admission.

condition of hypoxia resistance, expanding the use of WG as a potential antitumor drug.^{28,79,80}

Summary and perspectives

In the past few years, research on WG has improved dramatically. Currently, almost all types of cancer have been investigated to explore the effect of WG, especially in HCC and leukemia. Accumulating evidence shows that WG not only targets the key molecules, which play an important role in the development of tumors, but also enhances the anticancer effect of chemotherapeutic drugs. What is more, based on the explorations both in vitro and in vivo, WG has been approved for Phase I trials in the People's Republic of China, which is a milestone for its clinical use in the future. Figure 3 shows the procedures required for WG to be a clinically approved drug.

However, although WG has been identified to suppress the growth of multiple tumors and induce apoptosis, results are still limited in some tumors in in vitro investigations. Thus, it is extremely urgent to complete the pharmacokinetic data for WG. Meanwhile, existing results on synergistic and chemosensitizing effects are mostly based on 5-FU, etoposide, PTX, and adriamycin; therefore, future investigations need to search for other drugs that can interact with WG to enhance anticancer effects.

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Disclosure

The authors report no conflicts of interest in this work.

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