Review Article
Pharmacological Effects of Verticine: Current Status

Zhenhua Yin,1,2 Juanjuan Zhang,1,2 Qingfeng Guo,1,2 Lin Chen,1,2 Wei Zhang,1,2 and Wenyi Kang1,2

1Zhengzhou Key Laboratory of Medicinal Resources Research, Huanghe Science and Technology College, Zhengzhou 450063, China
2Henan Joint International Research Laboratory of Drug Discovery of Small Molecules, Zhengzhou 450063, China

Correspondence should be addressed to Wenyi Kang; kangweny@hotmail.com

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Verticine is the major bioactive constituent of Fritillaria as a kind of Traditional Chinese Medicine. Pharmacological researches have reported various benefits of verticine, including anticancer, anti-inflammatory, protecting against acute lung injury, tracheobronchial relaxation, antitussive, expectorant, sedative, and analgesic activities, in addition to inhibiting proliferation of cultured orbital fibroblast, angiotensin converting enzyme (ACE), and acetylcholinesterase (AChE) and inhibiting hERG potassium channels. The underlying mechanisms of verticine are still under investigation. This review will comprehensively summarize the metabolism, biological activities, and possible mechanism of verticine.

1. Introduction

Verticine (Figure 1) belongs to a kind of isosterol alkaloid, is the major bioactive constituent of Fritillaria as Traditional Chinese Medicine that is widely used as an antitussive and expectorant [1]. Pharmacological researches on verticine have reported its valuable benefits in a variety of diseases, especially its anticancer effect. In this paper, the pharmacological effects, including metabolism, antitumor, anti-inflammatory, protection against acute lung injury diastolic bronchus, inhibition of angiotensin converting enzyme, and acetylcholinesterase, antitussive expectorant, sedative analgesia, were summarized, which provides theoretical references for its clinical application.

2. Metabolism

Pharmacokinetics of verticine is closely related to its biological activity, and the metabolism is influenced by the mode of administration, sex, and animal types. Pharmacokinetic behavior of verticine can provide the theory reference for clinical medicine.

In rabbits model, the pharmacokinetics of verticine was different between the intragastric (ig) administration and intravenous (iv) administration (Table 1). The $t_{1/2}$ of ig administration was three times longer than that of iv administration, suggesting that there might be a reabsorption process after ig administration. However, it showed a very low bioavailability of 10.65%, which might be its low solubility in water, incomplete absorption, or metabolism of gastrointestinal enzymes and efflux pumps [2].

The pharmacokinetics of verticine was influenced significantly by sex. Verticine was eliminated slowly in the plasma of male Sprague-Dawley rat but not in female rats, and gender-related differences were also observed significantly in the pharmacokinetic parameters (Table 1). Drug concentration in blood and tissue in male rats was significantly higher except for several tissues, such as fat, muscle, and skin (data not given). Urinary cumulative excretion of verticine in female rats (0.12±0.04%) was lower than that of male rats (0.90±0.28%), and fecal cumulative excretion between female rats (0.23±0.06%) and male rats (0.27±0.06%) had no difference. Differences of sex-associated metabolism for verticine in rats are mainly due to sex-dependent expression and activity of drug metabolism enzymes and P-glycoprotein (P-gp) [3]. In addition, the main pharmacokinetic parameters of verticine were obviously different from [3] in Sprague-Dawley rats’ plasma after gastric gavage extract of Fritillaria thunbergii Miq. The V1/F was 40.832 L/mg, indicating that verticine was mainly distributed in blood, intracellular fluid,
and extracellular fluid, and it was widely distributed in vivo [4].

Further study showed that the intestinal absorption of verticine involved both active transport, facilitated diffusion, and resulted in the low bioavailability in male and female rats [34]. Caco-2 cell monolayer exerted an effect on the intestinal absorption of verticine. Verticine transport was concentration-dependent type, and both \( \text{P}_{\text{app(AP-BL)}} \) and \( \text{P}_{\text{app(BL-AP)}} \) were higher at 4°C than that at 37°C. When the P-glycoprotein (P-gp) inhibitors, verapamil, and cyclosporin A were present, the \( \text{P}_{\text{app(AP-BL)}} \) was higher and \( \text{P}_{\text{app(BL-AP)}} \) was lower, and the absorption permeability was not affected by EDTA-Na₂. The P-gp inhibitors could increase the absorption of verticine, and EDTA-Na₂ had no discernible effect on absorption. The intestinal absorption of verticine across Caco-2 cell monolayers involved active transport rather than passive diffusion, and verticine was a substrate of P-gp [35].

3. Pharmacological Effects

3.1. Antitumor Effect. The treatment of cancer is mainly based on chemotherapy. Multiple drug resistance limited the improvement of chemotherapy efficacy and also became an important reason for the recurrence and metastasis of cancer. Verticine had the effects of anti-cell proliferation and apoptosis in many human tumor cell lines and could reverse the multidrug resistance of some drug-resistant cell lines, such as breast cancer, leukemia, lung cancer, and gastric cancer cells.

3.1.1. Anti-Breast Cancer Effect. Verticine could inhibit the proliferation of breast cancer cell and induce its apoptosis and significant multidrug resistance reversal activity against breast cancer cell. Tong et al. confirmed that verticine had the effects of anti-cell proliferation and apoptosis in many human tumor cell lines and could reverse the multidrug resistance of some drug-resistant cell lines, such as breast cancer, leukemia, lung cancer, and gastric cancer cells.

\[ \text{A two-compartment model, } C_{\text{max}} = 43.7 \pm 22.7 \text{ ng/mL, } T_{\text{max}} = 1.5 \pm 0.7 \text{ h, } t_{1/2} = 4.2 \pm 2 \text{ h, } \text{AUC}_\infty = 214 \pm 84.6 \text{ ng/(mL/h), } \text{AUC}_\text{GFP} = 214 \pm 84.5 \text{ ng/(mL/h), CL/F} = 128.9 \pm 32.6 \text{ L/kg/h, V/F} = 78.3 \pm 305.6 \]

\[ \text{A three-compartment model, } C_{\text{max}} = 84.39 \pm 15.39 \text{ ng/mL, } \text{AUC}_\text{GFP} = 50.72 \pm 14.02 \text{ ng/(mL/h), } t_{1/2} = 2.19 \pm 1.07 \text{ h} \]

\[ \text{A two-compartment model, } C_{\text{max}} = 57.6 \pm 21.6 \text{ ng/mL, } T_{\text{max}} = 2.9 \pm 1.7 \text{ h, } t_{1/2} = 6.2 \pm 1.9 \text{ h, } \text{AUC}_\infty = 662.4 \pm 277.9 \text{ ng/(mL/h), } \text{AUC}_\text{GFP} = 665.3 \pm 213.3 \text{ ng/(mL/h), CL/F} = 41.5 \pm 20.1 \text{ L/kg/h, V/F} = 374.1 \pm 186.2 \text{ L/kg} \]

\[ C_{\text{max}} = 3.671 \pm 0.876 \mu \text{g/L, } T_{\text{max}} = 32.5 \pm 1.292 \text{ min, } t_{1/2} = 29.269 \pm 24.156 \text{ min, } t_{1/2} = 162.897 \pm 30.669 \text{ min, } \text{AUC}_\infty = 628.56 \pm 100.99 \mu \text{g/(L*min), } \text{AUC}_\text{GFP} = 630.87 \pm 102.136 \mu \text{g/(L*min), CL/F} = 0.423 \pm 0.075 \text{ L/min/kg, V/F} = 40.83 \pm 17.616 \text{ L/kg} \]

* \( P < 0.05 \), significantly different from female rats.

**Figure 1: Chemical structure of verticine.**

Table I: The pharmacokinetics of verticine in references.

| Models | Extracts/compounds | Methods | Mode of administration | Pharmacokinetic parameters | Ref. |
|--------|-------------------|---------|------------------------|----------------------------|-----|
| Rabbits | Verticine | LC-MS/MS | iv | A two-compartment model, \( C_{\text{max}} = 48.31 \pm 7.40 \text{ ng/mL, } \text{AUC}_\infty = 270.08 \pm 80.17 \text{ ng/(mL/h), } t_{1/2} = 6.38 \pm 3.11 \text{ h} \) A three-compartment model, \( C_{\text{max}} = 84.39 \pm 15.39 \text{ ng/mL, } \text{AUC}_\text{GFP} = 50.72 \pm 14.02 \text{ ng/(mL/h), } t_{1/2} = 2.19 \pm 1.07 \text{ h} \) | [2] |
| Sprague-Dawley female rats | 4.25 g/kg Fritillaria thunbergii Miq. Extract | LC-MS/MS | a single oral administration | \( C_{\text{max}} = 43.7 \pm 22.7 \text{ ng/mL, } T_{\text{max}} = 1.5 \pm 0.7 \text{ h, } t_{1/2} = 4.2 \pm 2 \text{ h, } \text{AUC}_\infty = 214 \pm 84.6 \text{ ng/(mL/h), } \text{AUC}_\text{GFP} = 214 \pm 84.5 \text{ ng/(mL/h), CL/F} = 128.9 \pm 32.6 \text{ L/kg/h, V/F} = 78.3 \pm 305.6 \) | [3] |
| Sprague-Dawley male rats | 4.25 g/kg Fritillaria thunbergii Miq. Extract (0.45 g/kg body weight) | RRLC-MS/MS | gastric gavage | A two-compartment model, \( C_{\text{max}} = 57.6 \pm 21.6 \text{ ng/mL, } T_{\text{max}} = 2.9 \pm 1.7 \text{ h, } t_{1/2} = 6.2 \pm 1.9 \text{ h, } \text{AUC}_\infty = 662.4 \pm 277.9 \text{ ng/(mL/h), } \text{AUC}_\text{GFP} = 665.3 \pm 213.3 \text{ ng/(mL/h), CL/F} = 41.5 \pm 20.1 \text{ L/kg/h, V/F} = 374.1 \pm 186.2 \text{ L/kg} \) | [4] |
mechanism was investigated on 4T1 cells, and the results showed that verticine could regulate blood viscosity, improve blood flow state, reduce the expression of u-PA, VEGF, and PAI-1 protein and the secretion of IL-8, reduce the infiltration of neutrophils, improve TFP-2 protein expression to promote tumor apoptosis, and inhibit angiogenesis and reduced cell transfer rate [8].

3.1.2. Anti-Human Leukemia Effect. Verticine could inhibit the proliferation of human leukemia cell and induce apoptosis of multidrug resistant leukemia; the mechanism was likely to be related to protein expression, redox imbalance, and caspase-3. In the early studies, verticine could inhibit the proliferation of HL-60 and K562 and reverse the multidrug resistance reversal activity against HL-60/ADR and K562/A02, which might be the increase of intracellular drug concentration and inhibition of P-gp protein expression in drug-resistant cells [5, 9]. ROS was an important signal molecule in cells, involved in many events, for example, cell proliferation, apoptosis, and multidrug resistance [39, 40]. It induced ROS explosion and reduced GSH content in tumor cell to inhibit tumor cell proliferation and induce apoptosis, which had an antitumor effect [41, 42]. This finding was consistent with that of Qi et al. (2017) who proved the effect of verticine on cell viability, proliferation, and apoptosis of human leukemia and the function of reactive oxygen species and redox imbalance in this process [10, 11]. Some alkaloids could activate caspase-3 and caspase-dependent cell apoptosis [43–45], and stimulating the ROS production of K562 cell could promote caspase-3 expression and induce apoptosis [46, 47]. Therefore, verticine might also activate caspase-3-related pathway in the process of stimulating ROS-induced apoptosis in K562/A02 cells.

3.1.3. Anti-Lung Cancer Effect. Lung resistance protein (LRP) was closely related to primary resistance to cisplatin (DDP). Excision repair cross-complement 1 (ERCC1) mRNA enhanced DNA repair capacity to mediate multidrug resistance of platinum drugs [48]. Yang et al. found that verticine could inhibit A549/DDP cell proliferation in a dose-dependent manner within 48 h treatment, and the reverse index was 3.73. After 48 h, cell apoptosis rate and LRP positive cell of verticine were 38.16±2.25 and (5.8±1.3)/HP, respectively. In addition, verticine could obviously decreased the expression levels of ERCC1 mRNA and LRP. It indicated that verticine could reverse MDR of A549/DDP cell line. Its mechanism might be apoptosis induction and downregulated expression of LRP and ERCC1 mRNA [12, 13].

3.1.4. Anti-Gastric Cancer Effect. Verticine could inhibit proliferation of SGC-7901 and SGC-7901/VCR, but had no obvious multiple drug resistance reversal effect [14].

3.2. Anti-Inflammatory Effect. Inflammation is a complex biological response mediated by activated inflammatory cells and immunocytes, involving a balance between proinflammatory and anti-inflammatory factors [15, 49]. Verticine showed anti-inflammatory effect. Zhang et al. proved that verticine could regulate inflammatory microenvironment of 4T1 breast cancer cell by controlling the release of inflammatory factors and decreasing the expression of mRNA [7]. Additionally, verticine could inhibit the gene and protein expression of MUC5AC mucin induced by EGF, PMA, or TNF-α, by directly acting on airway epithelial cells, and the production of MUC5AC mucin protein induced by EGF, PMA, or TNF-α. This finding was consistent with the traditional use of F. thunbergii as remedy for diverse inflammatory pulmonary diseases [16]. At the same time, Yi et al. confirmed that verticine significantly inhibited tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β, increased IL-10 production in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages, and inhibited the phosphorylation of p38, ERK and c-Jun N-terminal kinase (JNK) as well as decreased p65 and IkB, which indicated that verticine inhibited the production of inflammatory cytokines induced by LPS through blocking MAPKs and NF-κB signaling pathways [50]. Verticine could inhibit the production of proinflammatory cytokines, such as IL-6, IL-8, and TNF-α, reducing MAPKs phosphorylation and the nuclear NF-κB expression in PMACI-induced HMC-1 [17].

In addition, the activity of T cell is inhibited, which can also achieve anti-inflammatory effect; Kv1.3 potassium channels play a key role in the activation of T cells. Verticine could inhibit Kv1.3 channels in a concentration-dependent manner (IC_{50}=142.1 μM at 150 ms) [18].

3.3. Protection against Acute Lung Injury. The pathogenesis of acute lung injury was complex, but its essence was the damage of lung endothelial cells and alveolar epithelial cells caused by excessive inflammation [51, 52]. LPS can activate and amplify inflammatory reactions in the body, causing the accumulation of inflammatory cells in the lungs [53]. Verticine had protective effect on LPS-induced ALI in mice; the mechanism was related to the inhibition of the inflammatory factors, the downregulation of the phosphorylation level of MAPKs in the inflammatory response signaling pathway, and the reduction of NF-κB gene transcriptional intensity [19–23].

3.4. Tracheobronchial Relaxation and Antitussive Effects. Tracheal bronchial relaxation of verticine could be attributed to M receptor and calcium ions. Verticine showed strong inhibitory effect on the contraction of isolated tracheal strips of guinea pigs induced by carbachol; the results implied that the effect could be attributed to M receptor of the tracheal wall [24]. This result was consistent with that of Chan et al. who demonstrated the mechanisms of competitive antagonism of muscarinic pathway and also the inhibition of influx of calcium ions [25]. At the same time, verticine could also significantly elevate the concentration of cAMP in the HEK cells transfected with muscarinic M2 receptor plasmid [54]. However, verticine did not exhibit agonistic β2 receptor activity. It could be seen that the effect of verticine on diastolic bronchus was not produced by the agonist β2 receptor [55].

Generally, M receptor is inhibited, which could have a certain antitussive effect, and verticine is an active constituent
Table 2: The biological activities of verticine in references.

| Activities | Models | Biological activities | Action mechanism | Ref. |
|------------|--------|-----------------------|------------------|------|
| Anti-breast cancer | MCF-7 | Inhibit proliferation, reversing multidrug resistance | - | [4, 5] |
| | MCF-7/TAM | Inhibit proliferation (at 48 h $IC_{50}=191.16$ g/mL; at 72 h, $IC_{50}=138.30$ g/mL), induce apoptosis | Decrease expression of Bcl-2 | [6] |
| Anti-bone | 4T1 | Inhibit proliferation (at 48h, $IC_{50}=14.7 \mu g/mL$) | (1) Down-regulate TGF-β, VEGF and MCP-1 secretion, decrease TGF-β and VEGF mRNA expression, regulating its tumor inflammatory microenvironment. (2) Regulate blood viscosity, improve blood flow state, reduce the expression of u-PA, VEGE, PAI-1 protein and the secretion of IL-8, reduce the infiltration of neutrophils, improve TFPI-2 protein expression | [7, 8] |
| Anti-human leukemia | HL60, HL-60/ADR, K562, K562/A02 | Inhibit proliferation ($IC_{50}=288.27\pm34.23, 256.52\pm26.15, 320.80\pm36.52, 300.06\pm33.18, \mu g/mL$), reverse multidrug resistance | Increase intracellular drug concentration and inhibit P-gp protein expression | [5, 9] |
| Anti-human leukemia | K562/A02 | Inhibit the cell viability and induce apoptosis, different concentrations of verticine (100, 200, 400 mol/L) | Induce the ROS outbreak and increase the GSH content, redox imbalance | [10, 11] |
| Anti-lung cancer | A549/DDP | Inhibit proliferation, induce apoptosis, reversing multidrug resistance | Down-regulate expression of LRP and ERCC1 mRNA | [12, 13] |
| Anti-gastric cancer | SGC-7901 and SGC-7901/VCR | Inhibit proliferation | - | [14] |
| Anti-inflammatory effect | 4T1 | Regulate inflammatory microenvironment | Control release of inflammatory factors, such as TGF-β, VEGF, MMP-9, and MCP-1, decreasing the expression of TGF-β and VEGF mRNA | [6] |
| Anti-inflammatory effect | Confluent NCI-H292 cells | Remedy for inflammatory pulmonary diseases | Inhibit gene and protein expression of MUC5AC mucin induced by EGF, PMA or TNF-α by directly acting on airway epithelial cells | [15] |
| Anti-inflammatory effect | LPS-induced RAW264.7 macrophages | Inhibit production of inflammatory cytokines induced by LPS | Block MAPKs and NF-kB signaling pathways | [16] |
| Anti-inflammatory effect | HMC-1 Cells | Inhibit production of inflammatory cytokines anti-inflammatory | Regulate the Phosphorylation of NF-κB and MAPKs | [17] |
| Anti-inflammatory effect | HEK 293 | - | Inhibit Kv13 channels | [18] |
| Protection against acute lung injury | Mice | Protective effect on acute lung injury | Inhibit expression of TNF-α, IL-2, IL-6 and IL-8 and COX-2, promote the synthesis and release of SP-A, decrease the levels of PGE2 and NO. And, in addition, down-regulate phosphorylation level of MAPKs in the inflammatory response signaling pathway, and reduce NF-κB gene transcriptional intensity | [19–23] |
| Activities                      | Models                                      | Biological activities                                                                 | Action mechanism                                      | Ref.  |
|--------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------|-------|
| Relaxation                     | Isolated trachea strips of guinea pigs      | Inhibit contraction                                                                   | M-receptor                                             | [24]  |
|                                | Rat isolated trachea and bronchial          | Anti-choke effect for ammonium hydroxide-induced cough (4 mg/kg)                      | Increase tracheobronchial mucous secretion and decrease the viscosity of mucus | [26]  |
|                                | Guinea pig trachea                          | Anti-choke effect for mechanical stimulation-induced cough (4 mg/kg)                  | Increase tracheobronchial mucous secretion and decrease the viscosity of mucus | [26]  |
|                                | Cat superior laryngeal nerve                | Anti-choke effect for electrical stimulation-induced cough (4 mg/kg)                   | Increase tracheobronchial mucous secretion and decrease the viscosity of mucus | [26]  |
|                                | Mice                                         | Antitussive effect                                                                    | Block Nav1.7 ion channel (IC₅₀ = 27 ± 3 μM)            | [17, 26] |
|                                | Mice                                         | Sedative effect                                                                       | Block Nav1.7 ion channel (IC₅₀ = 27 ± 3 μM)            | [29]  |
|                                | Mice                                         | Analgesic effect                                                                       | Block Nav1.7 ion channel (IC₅₀ = 27 ± 3 μM)            | [17, 26] |
|                                | Mice                                         | Inhibit proliferation of cultured Orbital fibroblast                                 | Block Nav1.7 ion channel (IC₅₀ = 27 ± 3 μM)            | [30]  |
|                                | Thyroid-associated ophthalmopathy (TO) patients | Inhibit acetylcholine inhibitory activity (ACHE)                                       | Block ACEI activity in a dose-dependent manner          | [32]  |
|                                | Rat plasma                                   | Inhibit angiotensin converting enzyme (ACE)                                           | Block ACEI activity in a dose-dependent manner          | [31]  |
|                                | Human orbital fibroblasts                   | Inhibit hERG potassium channels                                                       | Block hERG peak tail currents with IC₅₀ = 9 ± 2.8 μM   | [35]  |
|                                | HEEK293 cell line                           | Inhibit hERG peak tail currents with IC₅₀ = 9 ± 2.8 μM                                 | Block hERG peak tail currents with IC₅₀ = 9 ± 2.8 μM   | [35]  |
of *Fritillaria* in relieving cough, which is related to acting on M receptor of tracheal smooth muscle to relax trachea and relieve tracheal spasm. For ammonium hydroxide induced cough in mice, mechanical stimulation of guinea pig trachea induced cough in guinea pigs, and electrical stimulation of cat superior laryngeal nerve induced cough in cats; verticine (4 mg/kg) had obvious antitussive effect. For mechanical stimulation induced cough in guinea pigs, the antitussive effect of verticine reached the peak at 30–60 min, and the antitussive effect could be sustained for about 1 h [26]. In addition, verticine could also significantly inhibit cough frequency and increase latent period of cough in mice induced by ammonia[27].

### 3.5. Expectorant and Sedative Effects

Verticine had expectorant and sedative effects. The effect was related to its ability to increase tracheobronchial mucus secretion and decrease the viscosity of mucus [27, 28]. Verticine could reduce the spontaneous activity of mice, inhibit the increasing of number of activities caused by caffeine, prolong the pentobarbital sleep time, and increase the sleep rate in mice[29].

### 3.6. Analgesic Effect

Verticine could inhibit writhing reaction induced by acetic acid in mice; at the concentration of 1 mg/kg, it had significant analgesic effect (P<0.05), and at the concentration of 2 mg/kg, it had very significant analgesic effect (P<0.01) [26]. Previous studies showed that traditional local anesthetics could play an analgesic role by nonselectively blocking the voltage-gated sodium channel subfamily, and selective Nav1.7 inhibitors were also demonstrated to be analgesic in animal models. Nav1.7 emerged as a potential target for the treatment of pain [56]. Verticine was able to block the Nav1.7 ion channel (IC$_{50}$ = 47±3.3 μM), which might be the analgesic mechanism of verticine [17].

### 3.7. Other Effects

Several studies showed that verticine also had other effects. Li et al. proved that verticine could inhibit the proliferation of cultured fibroblast of the thyroid-associated ophthalmopathy (TAO)-patients; the inhibitory effect was obviously better than that of the normal [30]. Verticine could inhibit the activity of ACE I in a dose-dependent manner (IC$_{50}$=312.8 μM), which might be responsible, at least in part, for the antihypertensive action [31]. Unfortunately it showed no appreciable AChE inhibitory activity at a concentration of 100 μg/mL, and the inhibition rate was only 25% [32]. In addition, verticine could inhibit the hERG peak tail currents with IC$_{50}$ value of 43.7 mM, and multiple results suggested that the inhibition was related to the channel inactivation. Further investigation showed that the mechanism of the inhibition was related to the mutation of Y652 to Alanine reduced sensitivity to verticine, which suggested that Y652 was an important binding site of hERG for verticine [33]. The main concern for cardiac safety determination is the possible inhibition of hERG ion channels. So, verticine should be used with caution to avoid its toxic effect on the heart.

### 4. Conclusions

The summary of metabolism and pharmacological researches of verticine shows that the mode of administration, dose, and gender have effects on metabolism, and verticine possesses multiple pharmacological effects that are summarized in Table 2. Verticine can control the expression of related proteins, inhibit inflammatory factors, and destroy redox balance to achieve antitumor effect. The mechanism of anti-inflammatory effect was related to MAPKs and NF-kB signaling pathways, and the protection against acute lung injury has close relation with anti-inflammatory effect. Acting on M receptor and inhibiting influx of calcium ions could inhibit tracheobronchial contraction, so as to play a role in relieving cough. The clinical studies of verticine remain somewhat elusive and show the risks of heart-safety.

In summary, verticine is a new potential plant-origin drug that has antitumor, anti-inflammation, protecting liver injury, and antitussive effect. The clinical effect should be focused on.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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