

STUDY ON THE PHARMACOLOGICAL AND TOXICOLOGICAL MECHANISMS OF NUX VOMICA

Joanna Martina
Saint Petersburg State University, Stary Petergof 198504, Russia.

Abstract: This review systematically reviews the research progress on the pharmacology and toxicity mechanisms of Nux Vomica, including its botany, phytochemistry, pharmacology and toxicology. So far, 84 compounds have been isolated and identified from Nux vomica, including alkaloids, iridoid glycosides, flavonoid glycosides. The main toxic components are strychnine and strychnine. These compounds have a series of biological activities, including effects on the nervous system, analgesic effects and anti-tumor effects, and can inhibit the growth of pathogenic microorganisms and regulate immune function. Among them, the anti-tumor effects need to be studied. A preliminary study was also conducted on the methods of reducing toxicity and increasing efficacy of Nux Vomica.

Keywords: Strychnos vomica; Botany; Phytochemistry; Pharmacology; Toxicology; Strychnine; Anticancer; Methods of reducing toxicity and increasing efficacy

1 RESEARCH ON THE BOTANY, PHYTOCHEMISTRY, PHARMACOLOGY AND TOXICOLOGY OF NUX VOMICA

Nux vomica was first recorded in "Compendium of Materia Medica", and is also known as Strychnos vomica. The traditional medicinal part of the Nux vomica plant is its seeds, called Nux vomica. Zhang Xichun's evaluation of Nux vomica in "Medicine in Chinese Medicine and Western Records" is that "the power of opening meridians and penetrating joints is far better than other medicines." However, because of its high toxicity, the difference between the therapeutic dose and the toxic dose is only a millimeter. have many limitations in clinical application. Therefore, research on the pharmacology and toxicity mechanism of Nux vomica has been the focus of attention in recent years, aiming to explore a reasonable method of reducing toxicity and increasing efficacy to ensure the safety of medication and maximize its efficacy. The toxicity of Nux vomica is mainly concentrated in the seeds, and the main toxic components are strychnine (brucine) and strychnine (strych-nine) and other alkaloids [1].

According to "Medical Toxicology", taking 5 to 10 mg of strychnine can cause death [2]. It is recorded in the "Principles of Clinical Toxicology" that 15 mg for children and 30 to 100 mg for adults can be fatal [3]. Therefore, the lethal dose may be related to the age, gender and health status of the patient. Studies have shown that the toxicity of strychnine is 8 to 30 times that of strychnine. The toxic dose of strychnine for humans who accidentally consumes strychnine is 2 mg, and the lethal dose is 30 to 100 mg. In many studies, strychnine is mainly used. Changes in the content of xanthophylline are used as toxicity evaluation indicators [4]. Clinically, the initial symptoms of Nux vomica poisoning include headache, dizziness, nausea, vomiting, anxiety and mild convulsions, followed by general convulsions, giggling, trismus, opisthotonus, difficulty swallowing and breathing, and finally Causing respiratory arrest. In traditional Chinese medicine, the seeds of Nux Vomica are processed and used as medicine. They are bitter in taste and cold in nature. Its seed extract is commonly used in Western medicine as a central nervous system stimulant. Nux vomica has long been used to treat indigestion, chronic rheumatism, neurological diseases, and urinary incontinence. 17 century, nux vomica was introduced to the United States and some European countries, where it was often sold in powder form for the purpose of poisoning rats and other rodents. About two centuries ago, researchers discovered strychnine and strychnine from Nux Vomica, and people had a better understanding of their pharmacological effects. After that, Nux Vomica was gradually used in the pharmaceutical industry [5]. Nux vomica and its preparations are recorded in pharmacopoeias of many countries, including the United States Pharmacopeia and the British Pharmacopeia. These preparations include powdered medications, tinctures, and liquid extracts. For subcutaneous and oral administration, there are 3 salts: sulfate, nitrate, and hydrochloride. Available strychnine salts. In addition to official preparations, strychnine and strychnine are also used in unofficial preparations, and are used more in China, India and some Southeast Asian countries. In recent years, researchers have gradually discovered that strychnine has a variety of medicinal effects [6], including: analgesia. The analgesic effect of strychnine is likely to be related to its sedative effect and paralysis of sensory nerve endings. Non-addictive; anti-inflammatory and immunomodulatory, strychnine can be used to treat ankylosing spondylitis, rheumatoid arthritis and other immune diseases; Anti-tumor effect, Nux vomica has good meridians and analgesic effect, is widely used in clinical treatment of some pain, and also shows good effect in the treatment of cancerous tumor pain; protects cardiovascular, can hinder the formation of blood clots Formed, Nux Vomica Nitrogen Oxide and Nux Vomica have a protective effect on myocardial cells, which is beneficial to improving microcirculation and increasing blood flow. Due to the specific toxicology of Nux vomica, how to use new dosage forms or new technological methods to minimize or eliminate the damage caused by its toxicity to the human body, and at the same time, give full play to the therapeutic effect of Nux vomica will be a question. A very challenging and potential research direction.

1.1 Botany

Nux vomica belongs to the family Strychnaceae. It mainly grows in tropical mountains, valleys and humid areas and tropical limestone areas. It likes a tropical humid climate and is suitable for growing in calcareous loam or slightly acidic clay. It is distributed in Sri Lanka, India, Australia, and the Philippines., Myanmar, Thailand and other countries, it is cultivated in Fujian, Hainan, Guangxi, Guangdong, Taiwan, Yunnan and other provinces in China. It is a shrub or small tree, 5 to 25 m high. The leaves are folded in half, papery, nearly round, broadly oval or oval, 5 to 18 cm long and 4 to 13 cm wide. The flowers are usually white, and the fruit is a brown-yellow berry the size of a small orange. The pulp is gelatinous and contains 3 to 5 seeds. The dried mature seeds are disc-shaped, slightly concave, and very hard, with a diameter of 1.5 to 3 cm and a thickness of 3 to 6 mm. The seeds have dark gray endosperm, which is odorless but extremely bitter. The seeds are processed using hot sand processing methods and can be stored for a long time.

1.2 Botany

Almost all parts of the *nux vomica* plant have been studied, including seeds, leaves, flowers and stem bark. Many compounds have been isolated and identified from *Nux vomica*, including alkaloids, iridoid glycosides, flavonoid glycosides, triterpenes, steroids, organic acids. [7]. Among them, alkaloids are the main chemical components of this plant. Among these alkaloids, strychnine (chemical formula $C_{21}H_{22}N_2O_2$, molecular weight 334.1681) and strychnine (chemical formula $C_{23}H_{26}N_2O_4$, molecular weight 394.1893) are considered to be the main biologically active substances and toxic compounds. It is recorded in the ancient book "Compendium on Materia Medica": The tree is as big as a soft-shelled turtle, round and flat in shape, with white hair and a bitter taste. Birds that are poisoned by it will suffer numbness, convulsions, and death; dogs that are poisoned by it will suffer from heartache and death. If taken by mistake, it can cause cramping of the limbs. From this, it is not difficult to discover the highly toxic effect of strychnine.

1.3 Pharmacological Activity

According to the "Chinese Pharmacopoeia", *Nux Vomica* is bitter in taste, warm in nature, and returns to the liver and spleen meridian. It has been proven to eliminate blockages, reduce pain and inhibit swelling [8]. However, *Nux vomica* is highly toxic and should be processed before oral administration. It should not be taken for a long time. The dosage needs to be strictly controlled. Pregnant women are not allowed to take it. During the Ming and Qing Dynasties in China, *Nux Vomica* was mostly available in powder or pill form. According to the 2015 edition of the "Chinese Pharmacopoeia", many prescriptions now use strychnine. In the processing formula of strychnine powder, the content of strychnine is about 0.78% ~ 0.82%, and the content of strychnine is about 0.78% ~ 0.82%. Not less than 0.50%. In traditional Chinese medicine, *Nux Vomica* is often used in combination with frankincense, myrrh, skullcap, and safflower to treat fractures with congestion, swelling, and pain, such as Jiu San, Bali San and other traditional Chinese medicine prescriptions. In the treatment of rheumatism, spasm and numbness, *Nux vomica* is often used in combination with frankincense, myrrh, ephedra., such as *Nux vomica* powder, rheumatism *nux vomica* tablets, Tongbi tablets and other traditional Chinese medicine prescriptions. In these prescriptions, processed *nux vomica* is used.

1.3.1 Stimulating effect on the nervous system

Strychnine and strychnine are two important alkaloids in *Nux Vomica*. They are both powerful stimulants of the spinal cord and help promote the secretion of gastric juices and increase sensory awareness. Therefore, *Nux vomica* can make the response center of the central nervous system more sensitive to incoming stimuli [9]. Strychnine and strychnine have 3 important functions that may be related to the nervous system. *Nux vomica* can be used as a stimulant for the digestive tract, promoting intestinal peristalsis, causing the intestinal chylous ducts to absorb nutrients from food, and causing feces to be retained in the large intestine, which is very useful in the treatment of complete diarrhea. However, this effect is usually used in veterinary medicine and is rarely used in human treatment. *Nux vomica* can be used as a respiratory and circulatory stimulant, especially in cases of weakness [2]. *Nux vomica* can be used for paralyzed patients with motor nerve dysfunction; in terms of this function, *Nux Vomica* has been used in clinical treatments of traditional Chinese medicine, such as Zhen Cai Wan and Bu Nao Zhen Ao Decoction. Research in recent years has shown that cerebral infarction can be treated by using the principle of *Nux vomica* to promote the recovery of neurological function and increase the excitability of the spinal cord [10]. In addition, *Nux vomica* tincture can be used to treat heart failure. Its mechanism of action may be to stimulate the motor center and ganglion system, thereby treating patients with pulmonary circulation obstruction and right heart congestion.

1.3.2 Analgesic and anti-inflammatory effects

The application of *Nux vomica* in traditional Chinese medicine is closely related to its analgesic and anti-inflammatory effects, especially in the treatment of rheumatic bone pain, muscle pain, joint injury pain. There are many prescriptions for treating pain, such as Jiu San, Ma Qian San, Bali San, *Nux Vomica* San. Studies have shown that: due to interleukin-1 (IL-1) and prostaglandin E2 in experimental rats (PGE2), interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α) levels are reduced. It can be inferred that the mechanism of action of *Nux vomica* may be related to inhibiting the release of inflammatory mediators [11-12]. In addition, *Nux vomica* can significantly inhibit the degree of foot swelling and polyarthritis index levels in rats with adjuvant arthritis, and reduce joint pathological damage [13]. In the hot plate test, twisting test, and formalin test, it was found that strychnine and strychnine nitrogen oxide have significant

analgesic effects on pain caused by physical and chemical stimulation. In addition, they can also significantly inhibit the release of prostaglandin E₂ in inflammatory tissues, and leads to a decrease in vascular permeability in the plasma of arthritic rats, a decrease in the content of 5-HT in the plasma, and an increase in the content of 5-HT-3-acetic acid. Therefore, its analgesic and anti-inflammatory effects involve central and peripheral nervous mechanisms [14].

1.3.3 Anti-tumor effect

According to the "Compendium of Materia Medica", *Nux Vomica* has the effects of removing blood stasis, dispersing stagnation, and relieving pain, and can "eliminate lumps." Studies have shown that: *Nux vomica* extract has varying degrees of inhibitory effects on a variety of tumors, including breast cancer, liver cancer, colon cancer, multiple myeloma. Its anti-tumor mechanism includes reducing vascular endothelial growth factor (VEGF), inducing apoptosis and producing cytotoxicity [15-16]. VEGF can induce angiogenesis in the body, which is key to tumor growth, invasion and metastasis. research shows: Strychnine significantly inhibited the development of mouse sponge implantation model (25, 50 mg·kg⁻¹·d⁻¹ for 9 d) and breast cancer bone metastasis nude mouse model (1.73, 3) by reducing the level of VEGF. 45, 6.90 mg·kg⁻¹·d⁻¹, lasting 8 d), can significantly inhibit angiogenesis [17]. Further studies have shown that strychnine blocks the production of VEGF by inhibiting the VEGF receptor 2 (VEGFR2) signaling pathway in vivo and in vitro [18]. Strychnine also significantly reduced the level of VEGF, thus inhibiting angiogenesis in mouse models [19]. Experiments have shown that the active ingredients and extracts of *Nux Vomica* induce apoptosis in different tumor cells by blocking the cell cycle or changing cell morphology. For example, *Nux vomica* water extract causes the growth of human gastric cancer AGS cells to be blocked [20], 1 μmol·L⁻¹ strychnine has an inhibitory effect on colon cancer cells in vitro [21]. Studies have shown that strychnine can block the cycle of human colon cancer cell SW480 in the G₂/M phase, thereby inhibiting the proliferation of colon cancer cell SW480 [22]. In addition, strychnine-induced cell morphological changes include tumor cell shrinkage, chromatin condensation, and tumor cell nuclear fragmentation. The report found: The ethanol extract of *Nux vomica* changed the morphology of tumor cells, and strychnine induced the morphological changes of tumor cells [23-24]. Strychnine causes significant cell growth arrest and has a certain inhibitory effect on human liver cancer cells [25]. In addition, animal experiments have shown that: strychnine (12.5, 25, 50 mg·kg⁻¹, lasting 14 days) It can prolong the survival time of mice with Ehrlich ascites cancer, and strychnine (5, 15 mg·kg⁻¹ for 12 days) can inhibit the migration and metastasis of hepatocellular carcinoma cells [26-27]. Recently, in vitro animal experiments have also found that *Nux vomica* can inhibit the activity of osteoclasts, reduce bone damage, and reduce the degree of cancer pain in mice undergoing breast cancer bone metastasis experiments [28]. Some studies have used human liver cancer HepG2 cells as the research object, and found through experiments that: within a certain range, with the passage of time and the increase in strychnine concentration, the apoptosis rate of liver cancer cells also increases [29]. Therefore, *Nux vomica* achieves its anti-tumor effects mainly by inducing apoptosis of cancer cells and preventing cancer cell metastasis. 1. 3. 4 Inhibition of microbial growth and immunomodulatory effects The ethyl acetate extract of *Nux vomica* bark has inhibitory effects on both G⁺ bacteria (such as *Bacillus subtilis* and *Staphylococcus aureus*) and G⁻ bacteria (such as *Escherichia coli* and *Pseudomonas aeruginosa*) [30]. *Nux vomica* has shown certain immunomodulatory effects in animal experiments. 30 mg·kg⁻¹ Strychnine can inhibit T lymphocyte proliferation and reduce ear swelling, but has no significant effect on spleen and thymus index [31]. It can be inferred from this that strychnine has a cellular immunosuppressive effect, but it has no obvious effect on immune organs. The terpenoids in *Nux vomica* leaves have certain immunosuppressive activity [32]. In addition, a study on the mechanism of the effect of *Nux vomica* on experimental autoimmune myasthenia gravis in rats found that: in processed *Nux vomica*, the level of acetylcholine receptor antibodies was reduced, and the levels of transforming growth factor β₁ (TGF-β₁) content, thus maintaining the dynamic balance between immune activation and immune suppression [33]. These studies suggest that *nux vomica* may be helpful in treating a variety of autoimmune diseases, including rheumatoid arthritis and myasthenia gravis.

1.4 Toxicology

In the Chinese Pharmacopoeia, *Nux Vomica* is listed as a highly toxic drug. Large doses of *Nux Vomica* can cause convulsions and death. Strychnine is highly toxic to the human body and can be rapidly absorbed from the gastrointestinal tract, acting on the central nervous system and causing general central nervous system excitement. Death from strychnine poisoning is usually caused by respiratory muscle spasm or central nervous system failure and is characterized by violent convulsions in which large numbers of muscles begin to move violently, even resulting in jaw locking, followed by stiffness, fatigue, and pain Or limbs torn, severe cases can lead to death. In addition to convulsions, *nux vomica* poisoning can also cause restlessness and slight acceleration of breathing, rapid pulse and strabismus, and even cardiac arrest [34]. In addition, long-term low-dose abuse of *Nux vomica* can induce delirium tremens and spasmodic pain in the abdomen and legs [2]. In view of the high toxicity of *Nux vomica*, it is crucial to explore its detoxification methods and mechanisms. At present, the detoxification and effectiveness of *Nux vomica* can be achieved mainly through the following ways.

1.4.1 Processing

In the traditional processing technology, *Nux vomica* seeds are often placed in heated sand, and the sand is continuously screened until the seeds swell and turn brown [35]. You can also use the deep-frying method, put pure sesame oil into a pot and heat it to about 230 °C, put the *nux vomica* into the pot, fry it until yellow, remove the oil immediately, and you can get [36]. In addition, some studies have used the method of soaking *nux vomica* seeds in milk, soaking *nux vomica*

seeds in milk for 24 hours. Finally, use a knife to scrape off the outer coating, then cut it into small pieces and boil it in milk for 3 days, about 4 hours a day. After 3 days, it is dried in a cool place and fried with beef ghee to be used as a therapeutic medicine [37]. In addition to the above processing methods, there are other processing methods, including vinegar boiling method and Indian aloe vera or ginger juice soaking method [38]. Some studies have also shown that the processing mechanism of strychnine into nitrogen oxide derivatives can effectively reduce the toxicity of strychnine [39]. Animal experiments also show that the hot sand treatment method can significantly reduce the toxicity of *Nux Vomica*. In mice, the LD50 values of *Nux Vomica* seeds after crude and hot sand treatment were 87.40 respectively., 109.01 mg·kg⁻¹ [40].

1.4.2 Compatibility

Compatibility is another common and important detoxification method of *Nux vomica*, such as compatibility with licorice, *Atractylodes*, Sappan wood, white peony root and other herbs. "Suwen Zangqi Fashi Lun" states that "the liver is painful and urgent, eat sweet food to relieve it". The symptoms of *Nux Vomica* poisoning are caused by liver wind. The use of sweet medicine to alleviate and reduce the poison is in line with the treatment methods mentioned in the "Nei Jing", and the sweet medicine can play an auxiliary role in analgesic. Research has found that the compatibility of *Nux vomica* and licorice can reduce the content of strychnine in the decoction, and the content reduction rate is positively correlated with the proportion of licorice [41]. Repeated administration of glycyrrhizic acid can accelerate the clearance of strychnine from the brains of mice after taking strychnine [42]. In addition, a study on the combination of *Atractylodes Rhizoma* and *Strychnos vomica* found that: compared with the single decoction of *Nux vomica*, the decoction of *Nux vomica* and *Atractylodes* (the best ratio for reducing toxicity is 1:6), strychnine and strychnine Alkali were reduced by 29.0% and 16.6% respectively [43]. The HPLC method was used to measure the content of the main alkaloid components before and after compatibility. The results showed that compatibility with hematoxylin can significantly reduce the content of strychnine, and the reduction rate is positively correlated with the proportion of hematoxylin used. During the general decoction process, the combination of *Nux vomica* and Sappan wood will produce a large amount of purple-black precipitate, which is said to be the result of the reaction between the alkaloids in *Nux vomica* and the amino acids and tannins in Sappan wood [44]. The compatibility of *Nux vomica* and ginger juice can reduce the mortality rate of experimental mice and improve liver cell edema and fatty degeneration, indicating that the compatibility of *Nux vomica* and ginger can alleviate the damage to the liver during long-term medication of *Nux vomica* [45].

1.4.3 Total alkaloid optimization method

The anti-inflammatory and analgesic effect of strychnine is weak but the toxicity is strong. Removing the strychnine in *Nux Vomica* will help reduce its toxicity and increase its effectiveness [46]. Due to the large difference in solubility between strychnine and strychnine in 50% ethanol solution, 50% ethanol solution was used to remove strychnine from the total alkaloids in *Nux vomica* and optimize the total alkaloids in *Nux vomica* to achieve reduction. The purpose of poisoning and enhancing efficacy [47].

1.4.4 New dosage form

As a fat-soluble component, strychnine has the characteristics of short half-life and low bioavailability. Therefore, using different carriers and optimizing the preparation process can improve the sustained release and targeting of the drug, thereby reducing the risk of strychnine. subtoxicity purposes. In recent research reports, several penetration enhancers (N, N-dimethylformamide, propylene glycol, azone, menthol) have been used as subjects to study their effect on strychnine and strychnine in strychnine cataplasm. The penetrating effect of strychnine. Results: 5% N, N-dimethylformamide had the best penetration-promoting effect [48]. In addition, some studies have shown that strychnine nanostructured lipid carriers can prolong the residence time of strychnine in rat models, thereby playing a long-term sustained release effect and achieving the purpose of reducing toxicity and increasing efficacy [49]. In summary, adopting certain processing methods or combining them with other Chinese herbal medicines, optimizing total alkaloids, and developing new dosage forms and new processes are important ways to explore the mechanism of attenuation and effectiveness of *Nux Vomica*, and how to accelerate the detoxification of toxic substances in it. Clearance is an important future research direction.

2 OUTLOOK

Although *Nux Vomica* is a poisonous traditional Chinese medicine, it has made outstanding contributions in the treatment of clinical diseases. A large number of studies have been made to ensure the safety of *Nux Vomica* medication and to ensure the efficacy of *Nux Vomica*. Among the components isolated and identified from *Nux vomica*, in addition to some bisindole alkaloids isolated from stem bark or roots, other compounds isolated from leaves and fruits, such as flavonoid glycosides, triterpenes, steroids. Phosphates and organic acids are also widely found in other plants and are not specific or representative. Therefore, research on *Nux Vomica* should pay more attention to the alkaloids in its seeds. In addition, although the inhibitory effect and immunomodulatory effect of strychnine on pathogenic microorganisms enriches its pharmacological effects, it should not be the focus of future research. The pharmacological activity (especially anti-tumor effect) and toxicology (especially anti-tumor effect) of strychnine It is a new method of reducing toxicity and increasing efficiency) and is still a key research direction. In terms of reducing toxicity and increasing efficacy, modification of chemical groups may make strychnine derivatives more effective and less toxic. Using chemically synthesized new drugs to replace natural strychnine may be a promising topic in future research. a potential direction. Biological activity-oriented isolation strategies and methods for attenuating the toxicity

and increasing the efficacy of *Nux vomica* should be the focus of future research. At present, the most important application of *Strychnos vomica* in traditional Chinese medicine is as an analgesic. However, due to the obvious clinical anti-tumor effect of *Strychnos vomica* and the urgent need for effective anti-cancer drugs, the anti-tumor mechanism of strychnine should be further research has been conducted on the anti-tumor activity of *Nux Vomica* with different drug combinations and different doses. In addition to conducting molecular experiments *in vitro*, anti-tumor tests should also be combined with *in vivo* experimental results to accurately evaluate its anti-tumor effect.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

REFERENCES

- [1] CHEN J, WANG X, QU YG. Analgesic and anti-inflammatory activity and pharmacokinetics of alkaloids from seeds of *Strychnos nux-vomica* after transdermal administration: Effect of changes in alkaloid composition. *J Ethnopharmacol*, 2012, 139(1): 181-188.
- [2] RODGERS GC. *Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning*. J Am Med Association, 1997, 278(14): 1201-1201.
- [3] GOSSEL TA. *Principles of Clinical Toxicology*[M]. 3rd ed. Raven Press, New York, 1994:421.
- [4] Jia Gongfu, Li Tao, Xu Li. *Handbook on the Prevention and Treatment of Drug Toxic and Side Effects*[M]. Beijing: China Union Medical College Press, 2004.
- [5] MCINTOSH RA. *Nux Vomica and Its Uses*. *Can J Comp Med Vet Sci*, 1940, 4(5): 125-127.
- [6] Li Chaoyang, Qiu Haiyan, Lou Yuqian. Experimental study on the anti-inflammatory and analgesic effects of cinnamon and cinnamon twig on the anti-inflammatory and analgesic effect of *Nux Vomica*. *Rheumatism and Arthritis*, 2013, 2(5): 17-20.
- [7] ZHANG JY, LI N, HU K. Chemical constituents from processed seeds of *Strychnos nux-vomica*. *J Chin PharmSci*, 2012, 21(2): 187-191.
- [8] MOHAMED MAD, Omayma AE. Phytochemical study, cytotoxic, analgesic, antipyretic and anti-inflammatory activities of *Strychnos nux-vomica*. *Cytotechnology*, 2015, 67 (5): 831-844.
- [9] CAI BC, WANG TS, KUROKAWA M. Cytotoxicities of alkaloids from processed and unprocessed seeds of *Strychnos nux-vomica*. *Acta Pharmacol Sinica*, 1998, 19 (5): 425-428.
- [10] Chen Gencheng, Xu Songhu. Experimental study on the treatment of cerebral infarction by *Nux Vomica*. *Journal of Cardiovascular and Cerebrovascular Diseases of Integrated Traditional Chinese and Western Medicine*, 2012, 10(1):75-76.
- [11] Tang Yingxue, Liu Ye, Liang Xiaodong. Analysis of the effect and mechanism of *Nux Vomica* combined with white peony root on anti-inflammatory immunity in rats with adjuvant arthritis model. *Shandong Journal of Traditional Chinese Medicine*, 2014, 33(8): 660-662.
- [12] Xu Lijun, Wei Shichao, Lu Fuler. Comparative study on the treatment of experimental arthritis with several components of *Nux Vomica*. *Journal of Tongji Medical University*, 2001, 30(6): 564-565.
- [13] Zheng Yongqiu, Wu Zhenzhen, Liu Jianxun. Therapeutic effect of *Nux Vomica* total base vesicle gel on AA rats. *Chinese Journal of Traditional Chinese Medicine*, 2012, 37 (10): 1434-1439.
- [14] YIN W, WANG T S, YIN F Z. Analgesic and anti-inflammatory properties of brucine and brucine N-oxide extracted from seeds of *Strychnos nux-vomica*. *J Ethno-pharmacol*, 2003, 88(2-3): 205-214.
- [15] LIU F, WANG XL, HAN X. Cytotoxicity and DNA interaction of brucine and strychnine-two alkaloids of *Semen Strychni*. *Int J Biol Macromol*, 2015, 77:92-98.
- [16] DENG XK, YIN FZ, LU XY. The apoptotic effect of brucine from the seed of *strychnos nux-vomica* on human hepatoma cells is mediated via Bcl-2 and Ca²⁺ involved mitochondrial pathway. *Toxicol Sci*, 2006, 91(1): 59-69.
- [17] AGRAWAL SS, SARASWATI S, MATHUR R. Brucine, a plant derived alkaloid inhibits inflammatory angiogenesis in a murine sponge model. *Biomed Preventive Nutrition*, 2011, 1(3): 180-185.
- [18] SARASWATI S, AGRAWAL SS. Brucine, an indole alkaloid from *Strychnos nux-vomica* attenuates VEGF-induced angiogenesis via inhibiting VEGFR2 signaling pathway *in vitro* and *in vivo*. *Cancer Lett*, 2013, 332(1): 83-93.
- [19] SARASWATI S, AGARWAL SS. Strychnine inhibits inflammatory angiogenesis in mice via down regulation of VEGF, TNF- α and TGF- β . *Microvasc Res*, 2013, 87:7-13.
- [20] LEE SM, KWON JI, CHOI YH. Induction of G2 / M arrest and apoptosis by water extract of *Strychni Semen* in human gastric carcinoma AGS cells. *Phytother Res*, 2008, 22(6):752-758.
- [21] Li Li, Wang Chun, Lu Hongda. Strychnine induces apoptosis in colon cancer SW480 cells by inhibiting the IL-6/STAT3 signaling pathway. *Chinese Journal of Pathophysiology*, 2016, 32(6): 998-1003.
- [22] Wang Wenjia, Si Fangying, Zhao Fei. Study on the effect and mechanism of strychnine on the proliferation and cycle of human colon cancer cell SW480. *Chinese Journal of Traditional Chinese Medicine*, 2020, 38(8): 106-109.
- [23] RAO PS, PRASAD MNV. *Strychnos nux-vomica* root extract induces apoptosis in the human multiple myeloma cell line- U266B1. *Cell Biochem Biophys*, 2013, 66 (3): 443- 450.

- [24] DENG XK, YIN W, LI WD. The anti-tumor effects of alkaloids from the seeds of *Strychnos nux-vomica* on HepG2 cells and its possible mechanism. *J Ethnopharmacol*, 2006, 106(2): 179-186.
- [25] YIN W, DENG XK, YIN FZ. The cytotoxicity induced by brucine from the seed of *Strychnos nux-vomica* proceeds via apoptosis and is mediated by cyclooxygenase 2 and caspase 3 in SMMC 7221 cells. *Food Chem Toxicol*, 2007, 45 (9):1700-1708.
- [26] AGRAWAL SS, SARASWATI S, MATHUR R. Cytotoxic and antitumor effects of brucine on Ehrlich ascites tumor and human cancer cell line. *Life Sci*, 2011, 89(5-6): 147-158.
- [27] SHU GW, MI X, CAI J. Brucine, an alkaloid from seeds of *Strychnos nux-vomica* Linn. , represses hepatocellular carcinoma cell migration and metastasis: The role of hypoxia inducible factor 1 pathway. *Toxicol Lett*, 2013, 222 (2):91-101.
- [28] Qiao Cuixia, Zhang Xinfeng, Cheng Xufeng. Effects of *Nux vomica* decoction on pain in mice with bone metastasis and osteoclasts in bone metastases. *Chinese Patent Medicine*, 2020, 42(7): 1907-1910.
- [29] Liang Xiaoting, Fan Guoquan, Ren Hua. Strychnine induces apoptosis of human liver cancer HepG2 cells via JNK-Fas pathway. *Chinese Medicine and Clinic*, 2017, 17(8): 1105-1108.
- [30] THAMBI M, CHERIAN T. Phytochemical investigation of the bark of *Strychnos nux-vomica* and its antimicrobial properties. *Pharma Innovation J*, 2015, 4(5):70-72.
- [31] Wang Lijie, Cai Baochang, Chen Jun. Effects of strychnine on immune function in mice. *Modern Chinese Medicine Research and Practice*, 2008, 22(6):42-44.
- [32] GUPTA A, CHAPHALKAR SR. Immunosuppressive activity of crude terpenoids from extracts of *Embllica officinalis*, *Ficus racemosa* and *Strychnos nux-vomica*. *Micromedicine*, 2016, 4: 1-7.
- [33] Zou Ying, Qiu Tao, Yang Feng. Study on the immunomodulatory mechanism of *Nux vomica* on experimental autoimmune myasthenia gravis rats. *Chinese Journal of Traditional Chinese Medicine*, 2015, 30(8): 2994-2998.
- [34] RAO K, NAYAK VC, JAMES RI. Survival after strychnine poisoning: A case report. *Res J Pharmacol Biol Chem Sci*, 2016, 7(1): 1769-1771.
- [35] Lu Jun, Liu Zhaolong, Zhao Feicui. Determination of strychnine and strychnine content in raw and processed products of *Nux vomica* and experimental study on toxicity. *Journal of Xinjiang Medical University*, 2020, 43(4): 506-509.
- [36] Yang Wenning, Liu Yang, Tang Mingmin. An overview of the processing methods and processing mechanism of *Nux Vomica*. *China Association of Traditional Chinese Medicine. Proceedings of the Ninth Academic Annual Conference of the Chinese Medicinal Chemistry Branch of the Chinese Society of Traditional Chinese Medicine (Volume 1)*, 2014:6.
- [37] KUMAR MA, J SUBRAT, O NISHA. A comprehensive review on effects of Sodhan karma (detoxification procedure) and therapeutic potential of visha-tinduka (*Strychnos nuxvomica*). *Int J Res Ayurveda Pharm*, 2012, 3 (2): 211-213.
- [38] KATIYAR C.KUMAR A.BHATTACHARYA SK. Ayurvedic processing seeds of *nux-vomica*: Neuropharmacological and chemical evaluation. *Fitoterapia*, 2010, 81(3): 190-195.
- [39] Wang Dandan, Li Junsong, Cai Baochang. Study on the content changes of strychnine and strychnine nitrogen oxides before and after processing of *Nux Vomica*. *Chinese Journal of Traditional Chinese Medicine*, 2009, 27(2): 435-436.
- [40] Wang Na, Xu Haijiang, Sun Tongwen. Acute toxicity test of raw, scalded and vinegar-boiled *nux vomica*. *Clinical Research of Traditional Chinese Medicine*, 2013, 5(4): 25-26, 28.
- [41] GU L.WANG X, LIU Z. A study of Semen *Strychni* induced renal injury and herb-herb interaction of *Radix Glycyrrhizae* extract and/or *Rhizoma Ligustici* extract on the comparative toxicokinetics of strychnine and brucine in rats. *Food Chem Toxicol*, 2014, 68:226-233.
- [42] Liu Yanwen, Yan Miao, Li Huande. Study on the effects of glycyrrhizic acid on the toxicokinetics and detoxification mechanism of strychnine. *Chinese Journal of Hospital Pharmacy*, 2012, 32(16): 1239-1243.
- [43] Liang Xiaodong. HPLC determination of changes in main alkaloid components before and after compatibility of *Nux vomica* and *Atractylodes rhizome*. *Chinese Journal of Traditional Chinese Medicine*, 2015, 33 (6): 1377-1379.
- [44] Liang Xiaodong, Tang Yingxue. HPLC determination of main alkaloid content changes of *Nux vomica* compatibility with hematoxylin. *Chinese Journal of Traditional Chinese Medicine*, 2014, 29 (4): 1101-1104.
- [45] Zhao Xue, Sun Jingchang, Tan Qi. Experimental study on the toxic effects of ginger on *nux vomica*. *Shandong Journal of Traditional Chinese Medicine*, 2016, 35(5): 462-463 + 467.
- [46] Liu Jun, Zhang Huizong. Methods to reduce the toxicity and increase the effectiveness of *Nux Vomica*. *Journal of Practical Traditional Chinese Medicine Internal Medicine*, 2015, 29(6): 159-163.
- [47] Li Jun, Yan Daonan. Preparation and evaluation of optimized total alkaloids from *Nux Vomica*. *China Medical Herald*, 2012, 9(36): 35-37.
- [48] Yu Tao, Feng Wei, Liu Yi. In vitro transdermal experiments of *Nux vomica* cataplasm and screening of penetration enhancers. *Chinese Journal of Hospital Pharmacy*, 2018, 38(3): 229-233.
- [49] Guan Qingxia, Zhang Yue, Zou Shujun. Comparative study on the pharmacokinetics of strychnine and its nanostructured lipid carrier in rats. *Chinese Pharmacy*, 2018, 29 (20): 2777-2781.