Proceedings of Anticancer Research

Research Article

Research Progress on Toxicity of Natural Compounds

Zhangping Zhou[1,2], Zilong Fu[3*], Yan Li[4], Biao Ren[2], Ling Duan[1], Song Teng[1], Zhuoxuan Liang[1]

[1]School of Public Health, Kunming Medical University, Kunming 650500, Yunnan Province, China

[2]Xi'an Xincheng District Center for Disease Control and Prevention, Xi'an 710000, Shaanxi Province, China

[3]The Second Affiliated Hospital of Xi'an Medical College, Xi'an 710038, Shaanxi Province, China

[4]Traditional Chinese Medicine Hospital of Xincheng District, Xi'an 710000, Shaanxi Province, China

Abstract: There are many active substances in natural resources. After years of research, researchers at home and abroad have extracted active compounds and proved that these compounds have low toxicity and high efficiency, but the toxicity of these compounds cannot be ignored. In this paper, the research progress on the toxicity of compounds isolated from various natural substances is reviewed, which provides a reference for the further development and rational utilization of natural compounds.

Key Words: Natural compounds; Toxicity

Publication date: March, 2021
Publication online: 31 March, 2021
[*]***Corresponding author:*** Zilong Fu,fuzilong@live.com

1 Introduction

In recent years, many studies have found that many active substances in natural resources have pharmacological effects, many of which have the advantages of strong targeting and small side effects[1]. However, most natural substances are mixtures, so it is particularly important to separate and purify the active parts of natural substances. Domestic and foreign scholars to purify the active parts of natural substances is conducive to large-scale processing and production, but its toxicity has attracted much attention. In this paper, the systemic toxicity and genotoxicity were classified, and the toxicity of each compound was introduced.

2 Reproductive system toxicity

2.1 Male reproductive toxicity

2.1.1 Andrographolide

Andrographolide is a compound extracted from Andrographis paniculata, which is used in the treatment of inflammation, virus infection, tumor and other diseases[2]. It is known as a natural antibiotic, but its adverse reactions include skin and mucous membrane, respiratory, digestive, cardiovascular, nervous system damage[3,4]. The main reproductive toxicity is that it has certain toxic effect on sperm and testis of mice. It can prevent sperm meiosis by blocking the energy source of sperm. Spermatogenic epithelial cells in mouse testis are destroyed, which makes spermatogenic cells unable to differentiate correctly, leading to sperm abnormalities[5].

2.1.2 Triptolide

Triptolide (triptolide, triptolide TP) is a compound purified from Tripterygium wilfordii, with molecular formula of c20h24o6, which can treat inflammation, allergic reaction, malignant tumor, etc[6]. Studies have shown that triptolide has a protective effect on cardiovascular disease and osteoporosis[7]. Reproductive toxicity is one of the main side effects of triptolide. The clinical manifestations of triptolide are decreased sperm or azoospermia in men, decreased menstruation or amenorrhea in women. Li Fan et al[8] used computer-aided sperm analysis (CASA) system to evaluate the sperm kinetic parameters of left epididymal tail after triptolide was given to rats. The results showed that the sperm

movement speed and linear direction of epididymal tail were changed. After 8 weeks of administration of triptolide by Ni et al[9], the content of triptolide in testis of SD rats was detected by LC / Ms. It was found that triptolide accumulated in testis, and the quality of testis and epididymis decreased significantly; These phenomena prove that long-term use of triptolide can lead to serious male reproductive toxicity. Liu et al[10] also found male reproductive toxicity after 28 days of triptolide administration in rats, characterized by testicular spermatogenic cell necrosis and exfoliation and lack of mature sperm in epididymis. The decrease of testicular marker enzyme activity hinders the aerobic metabolism and energy utilization of testicular tissue, forming a damage chain to male reproductive system. Liu et al[11] gave female SD rats triptolide for 90 days to observe the reproductive toxicity of triptolide. The results showed that the weight of ovaries and uterus was significantly reduced, the levels of estradiol (E2) and progesterone (P) in serum were significantly decreased, and the levels of follicle stimulating hormone (FSH) and luteal hormone (LH) were significantly increased in the middle and high dose triptolide group

2.1.3 Gossypol

Gossypol is a kind of yellow polyphenolic pigment in the organs of Gossypium plants of Solanaceae, which has anti-virus, anti-tumor, anti keratinocyte proliferation, anti-oxidation, anti-parasite and anti-autoimmune effects. It was found that after oral administration for 5 weeks, the number of seminiferous tubules and spermatogenic cells decreased. In some rats, the loss of spermatogenic epithelium and the shedding of immature spermatogenic cells were observed[12]. In the epididymis, gossypol breaks the acrosome of the sperm and separates the head from the tail. The mitochondrial spiral sheath in the middle of sperm becomes disordered and swollen. In addition, gossypol can significantly inhibit the activity of acrosin in sperm, thus reducing the chance of fertilization[13]. After two months of drug withdrawal, these pathological changes can automatically recover, and its antifertility effect is reversible[14]. Studies have found that it can cause atrophy of spermatogenic epithelium, a few damage may recover, but all damage will lead to permanent infertility.

2.1.4 Colchicine

Colchicine is the first alkaloid extracted from colchicine. In order to resist gout, hepatitis and tumor and treat various skin diseases, it can be used to treat acute attack of gouty arthritis and prevent joint injury caused by urate. However, colchicine has obvious toxicity], and can cause heart, liver, gastrointestinal, muscle, nerve, bone marrow and other diseases[16]. It can also inhibit sperm motility, induce sperm apoptosis and decrease serum testosterone.

2.2 Female reproductive toxicity

2.2.1 Inclusion criteria

Pinellia ternata protein is a bioactive protein in Pinellia ternata, which has rich medicinal value[17]. It can combine with the sugar structure on the cell membrane of mother or daughter to affect implantation, and Pinellia ternate protein can coagulate with hemoglobin to cause abortion[18]. By reducing the level of endogenous progesterone, it leads to ovarian luteal dysfunction, abnormal decidua, abortion, embryo stop development and death.

2.2.2 Toosendanin

Toosendanin is a tetracyclic triterpenoid compound in toosendan fruit, which has anti botulinum toxin, insecticidal effect, anti-tumor, calcium channel agonist, synaptic transmission blocker, antiviral effect[19]. It is also the only natural compound that can inhibit the growth of a variety of tumor cells, or induce its apoptosis[20]. In this study, toosendanin was injected intraperitoneally into mice on the 5th, 6th and 7th day of pregnancy Results the levels of interferon - γ and tumor necrosis factor - α were significantly increased. At the same time, the levels of CD4 + and CD8 + T lymphocytes in endometrium of toosendanin treated group were also increased, suggesting that a large number of immune cells invaded the uterus, which was the main cause of pregnancy failure, indicating its reproductive toxicity[21].

3 Digestive system toxicity

3.1 Hepatotoxicity

3.1.1 Toosendanin

The results showed that toosendanin had obvious hepatotoxicity. Xiong Yanhong[22] gave toosendanin to rats orally. The serum ALT levels of 62.6g/kg and 127.5g/kg groups were significantly different from

those of normal group (P<0.01). The mechanism of toosendanin induced hepatocyte death is that toosendanin induced mitochondrial dysfunction and activated caspase. Studies have shown that after intragastric administration of 60g / kg, the metabolism of toosendanin in rats is weakened, suggesting that there is liver and kidney damage, indicating that its hepatotoxicity is related to the accumulation in the body[23].

3.1.2 Emodin

Rhubarb is an important traditional Chinese medicine for the treatment of many diseases, which has a wide range of clinical applications. Modern studies have shown that Rhubarb Anthraquinones have anti-inflammatory, anti-tumor and cardiovascular protective effects. At the same time, emodin can induce apoptosis. This conclusion was first confirmed by the experiment of renal fibroblasts in patients with lupus nephritis. In addition, rhubarb also has protective effect on liver and kidney damage [25]. On the other hand, long-term administration of rhubarb has certain damage to liver and kidney function[26]. The main toxic components are emodin, rhein and aloe emodin. Liu Yi et al[27] found that Rhein can activate the abnormal expression of apoptosis related proteins and zebrafish phase I metabolic enzymes, leading to hepatocyte apoptosis and hepatotoxicity.

3.1.3 Xanthophyllin B

Huangyaozi is the dry tuber of Huangdu, which is often used in the treatment of scrofula, blood heat and bleeding, sore swelling, gall and other diseases. Dioscorea flavescens B (DB) is a compound extracted from the seeds of Dioscorea flavescens[28]. Studies have shown that Dioscorea flavescens B has anti-tumor and anti-inflammatory effects[29]. DB is a furan compound, and its hepatotoxicity is mainly manifested in the furan part of its structure. Li et al[30] investigated the main site of DB hepatotoxicity by chemical hydrogenation of DB furan ring instead of its furan and tetrahydrofuran group. The results showed that the furan part could induce liver injury in animals, that is, there was no liver injury in animals given the same dose of tetrahydrofuran.

3.1.4 Matrine

Matrine is a kind of monomeric alkaloid, which widely exists in Sophora plants. It has anti-inflammatory, anti-virus, anti-tumor, anti-ischemia-reperfusion, anti-liver fibrosis, anti-arrhythmia, hypolipidemic and other pharmacological effects[31]. In this study, 24.7 mg / kg matrine was given by gavage for 30 days. The results showed that the main toxic target organs of mice were liver, kidney and brain[32]. After a single administration experiment[33], it was found that three out of ten mice died when matrine was 180 m /kg. In addition, it has been reported in the literature that the mortality of mice treated with Matrine 200 mg/kg is 100%, and the liver tissue has obvious punctate necrosis and varying degrees of water deformation, the liver cells are swollen and crowded, the liver sinuses are compressed, and the cytoplasm has vacuolation[34]. Results the mortality and serum enzyme content of mice in high-dose matrine group were significantly increased, and the degree of morphological changes of hepatocytes was significantly increased, which indicated that matrine had hepatotoxic effect. In vitro hepatotoxicity study, it is concluded that matrine has certain hepatotoxicity[35]. Studies have shown that superoxide dismutase (SOD) and glutathione (GSH) in liver of mice decreased after administration, indicating its hepatotoxicity[36].

3.1.5 Triptolide

In clinical use of Tripterygium wilfordii preparation, abnormal liver function, hepatomegaly and increased alanine aminotransferase activity can be observed in poisoned patients, suggesting that liver injury caused by Tripterygium wilfordii preparation is mainly liver parenchymal cell injury. Chen et al[37] found that triptolide induced liver injury is highly correlated with development, metabolism, immune response, apoptosis and changes of liver cytoskeleton. At the cellular level, the compound can reduce the viability of human liver L-02 cells, down regulate the level of anti-apoptotic protein Bcl-2, and up regulate the levels of Pro apoptotic protein Bax and tumor suppressor protein p53[38]. It is suggested that the compound can induce apoptosis and lead to liver injury. Fu et al[39] were given triptolide orally to rats for 28 days. The liver related biochemical indexes and histopathological changes were detected, and the changes of mitochondrial respiratory chain were further detected. Histopathological examination showed that the treated rats developed cystic fatty liver, most of which were filled with many small fat vesicles. After intraperitoneal injection of triptolide,

the expression of CD68 on Kupffer cells was significantly up-regulated, and the serum level of tumor necrosis factor (TNF) was increased, which may be one of the mechanisms of acute liver injury induced by Triptolide[40].

3.1.6 Colchicine

Liver is the main metabolic site of colchicine and the target organ of toxicity. Colchicine exposure for 28 days can lead to liver function damage, liver tissue lesions, and significantly increase serum TBA and ALP levels in rats. The characteristic of liver toxicity is cholestasis[41].

3.1.7 Geniposide

Geniposide (geniposide) is a compound extracted from Gardenia jasminoides Ellis, which can be used to treat cardiovascular, hepatobiliary and other diseases, diabetes, Alzheimer's disease[42]. However, it has been reported that geniposide, as the main active ingredient of Gardenia jasminoides Ellis, has obvious hepatorenal toxicity[43]. Cheng Shenghui et al[44] after intragastric administration of Geniposide 1.2 g/kg, the liver function indexes of alt, AST, ALP and total bilirubin (TB) in serum of normal rats were significantly increased 24 and 48 hours later, and there was a certain time toxicity relationship. Histopathological examination also showed pathological changes such as inflammatory cell infiltration and hepatocyte necrosis in portal area.

3.2 Bile duct toxicity

3.2.1 Triptolide

Tripterygium wilfordii (celangulin) is a compound extracted from Tripterygium wilfordii. It is the first natural active product isolated from Tripterygium wilfordii. It has important pharmacological effects[45]. It has been processed and developed into a potential pharmaceutical preparation with antioxidant, anti-inflammatory, anti-angiogenesis and anti-cancer effects. Triptolide is a pentacyclic triterpenoid belonging to methylquinone group. Triptolide can be used in the treatment of autoimmune diseases, asthma, chronic inflammation, tumor and neurodegenerative diseases. Triptolide has also been proved to have excessive regulatory effect on obesity in mice[46]. Cholangiotoxicity can be produced by affecting the viability of bile duct cells, changing their migration ability, blocking cell cycle and promoting apoptosis[47].

3.3 Gastrointestinal toxicity

3.3.1 Triptolide

Triptolide can cause digestive system disorder. In laboratory studies, triptolide given intraperitoneally or orally to mice with LD50 showed obvious congestion at the bottom of stomach and irregular scattered ulcers in intestine[48]. In the study of the process of triptolide in vivo, it was found that triptolide was easily absorbed by the gastrointestinal tract, but the absorption was not complete. It is speculated that this may be the reason for the stimulation of triptolide on the gastrointestinal tract.

4 Toxicity of urinary system

4.1 Nephrotoxicity

4.1.1 Dauricine

Dauricine (Menispermine), a compound extracted from Menispermum dauricum, can treat hypertension, arrhythmia, myocardial ischemia, cerebral ischemia, malignant tumor and other diseases[49]. Dauricine has certain toxic effects on human normal hepatocytes, human embryonic kidney cells and human renal tubular epithelial cells, suggesting that Dauricine may be toxic to liver and kidney, and it is one of the material bases of hepatorenal toxicity of Radix Menispermi[50].

4.1.2 Rhein and emodin

Rhein can be used in the treatment of bacterial infection, allergy, malignant tumor and so on. It can induce apoptosis of HK-2 cells and has cytotoxic effect. There were four main types of pathological changes, namely, swelling of renal tubular epithelial cells, protein tubular type in the lumen of renal tubules, hyperemia and focal proliferation of lymphocytes. It can be seen that long-term administration of emodin can cause different degrees of kidney damage in mice, and the greater the dose, the stronger the toxicity[51].

4.1.3 Triptolide

Most studies found that the acute toxicity of triptolide, kidney damage is more serious. In acute toxicity test[52], the apoptosis related proteins in kidney of Wistar rats were significantly changed. Yang et al[53] gave SD rats triptolide 1 mg/kg once to induce acute

nephrotoxicity. The expression levels of Pro apoptotic protein Bax, bid and bad were significantly increased, while the expression level of anti-apoptotic protein Bcl-2 was significantly decreased. Histological examination showed that renal function was seriously damaged, most renal tubular epithelial cells were necrotic and apoptotic, and renal tubular obstruction. It is suggested that oxidative stress plays a key role in triptolide induced tubular epithelial cell necrosis and renal function injury.

4.1.4 Geniposide

Geniposide at a higher dose (300 mg / kg) can cause renal pathological damage in rats after oral administration for 3 days. At this dose, geniposide at a dose of 300 mg/kg can cause renal damage in rats. It can be seen that the renal index increases, renal tubular epithelial cells swell, degenerate and vacuolate[54]. It is suggested that high dose geniposide has obvious nephrotoxicity.

5 Circulatory toxicity

5.1 Cardiotoxicity

5.1.1 Triptolide

Tripterygium wilfordii preparations can cause cardiac dysfunction. The study found that long-term administration of triptolide to SD rats resulted in higher myocardial sensitivity[55]. The acute toxicity test showed that vacuolar degeneration was the main cause of swelling, and the subendocardial myocardium also changed significantly. It is speculated that the damage mechanism may be related to mitochondrial damage and cell membrane damage[56]. Li Hua et al[57] the changes of myocardial cells of neonatal rats at different doses before and after administration in cell analysis system (RTCA) for 20 hours showed that triptolide significantly inhibited the activity of myocardial cells at low concentrations, and inhibited the potassium channel encoded by human ether-a-go-go related gene (hERG) at medium and high doses, affecting the myocardial expression. These results indicate that triptolide inhibits the activity of cardiomyocytes.

5.2 Hematotoxicity

5.2.1 Triptolide

The toxicity of triptolide to the blood system is characterized by neutropenia, thrombocytopenia, leucopenia and Erythropenia. Long term toxicity study mice were given triptolide for 12 weeks, and the results showed that lymphocyte (lym), hemoglobin (Hgb), intermediate cell (MID), red blood cell (RBC) and white blood cell (WBC) in peripheral blood decreased significantly[58].

6 Conclusion

With the development of modern medicine, the progress of biomedical technology and the formulation of various laws and regulations, drug toxicology is highly valued in drug research and development, and runs through the whole process of drug research and development. In the process of new drug discovery and development, about 40% of drugs fail to enter the clinical stage due to toxicity, so drug toxicity is an important factor to determine the success of drug research and development.

The object of the above study is the purified single component, a natural active substance can contain thousands of different monomers. Therefore, it is not appropriate to abandon the use of natural compounds only because of the toxicity of some monomer components. In the process of multi drug combination, chemical reactions often occur in toxic monomers, leading to quantitative or qualitative changes. As long as the scientific and rational use of these substances, can enhance the pharmacological effect, reduce toxicity and adverse reactions. In addition, drug treatment is carried out under the guidance of basic medical theory, emphasizing the dialectical analysis of the whole disease. As long as doctors use it properly, toxic ingredients can also be therapeutic ingredients. Therefore, we must dialectically understand the toxicity of natural extracts, try to avoid adverse reactions, and make unremitting efforts to improve the safety of clinical application.

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