

# Advanced research on anti-tumor effects of amygdalin

## ABSTRACT

Malignant tumors are the major disease that cause serious damage to human health, and have been listed as the premier diseases which seriously threatened human health by World Health Organization (WHO). In recent years the development of antitumor drugs has been gradually transformed from cytotoxic drugs to improving the selectivity of drugs, overcoming multidrug resistance, development of new targeted drugs and low toxicity with high specificity drugs. Amygdalin is a natural product that owns antitumor activity, less side effects, widely sourced and relatively low priced. All these features make the amygdalin a promising antitumor drugs, if combined with conditional chemotherapy drugs, which can produce synergistic effect. In this paper, we summarized the pharmacological activity, toxicity and antitumor activity of amygdalin, mainly focused on the advanced research of amygdalin on its antitumor effects in recent years, providing new insights for the development of new anticancer drugs, new targets searching and natural antitumor mechanism investigations.

**KEY WORDS:** Amygdalin, anti-tumor, pharmacological activity, toxicity

## INTRODUCTION

Amygdalin is also called bitter apricot, laetrile, almond, it is a cyanogenic compounds and belongs to the aromatic cyanogenic glycoside group. Its molecular formula is:  $C_{20}H_{27}NO_{11}$ , the molecular weight is 457.42. The chemical structure is D-mandelonitrile- $\beta$ -D-glucoside-6- $\beta$ -glucoside, as shown in Figure 1. Amygdalin is widely distributed in plants, especially in the rosaceous plant seed, for example, apricot, peach, cherry, plum etc.<sup>[1,2]</sup> It can hydrolyze and generate prunasin and mandelonitrile under the glucosidase action, such as amygdalase and prunase, and ultimately decomposed into benzaldehyde and hydrocyanic acid (HCN). Amygdalin itself is non-toxic, but its production HCN decomposed by some enzymes is poisonous substance.<sup>[3]</sup> Numerous studies have documented that amygdalin has antitussive and antiasthmatic effects, as well as an effects on the digestive system. Moreover, the pharmacological effects also include antiatherogenic, inhibition of renal interstitial fibrosis, prevention of pulmonary fibrosis, resistance to hyperoxia induced lung injury, immune suppression, immune regulation, antitumor, antiinflammatory and antiulcer.<sup>[4-7]</sup> It has been used for the treatment of asthma, bronchitis, emphysema, leprosy, colorectal cancer and vitiligo.<sup>[5]</sup> Amygdalin were decomposed to hydrocyanic acid, which is an antitumor compound, and benzaldehyde, which can induce an analgesic action, therefore it can be used for the treatment of cancer and relieve pain.<sup>[8]</sup> Therefore the anti-tumor effect of amygdalin is one

of the hot topic in recent years. It has anticancer function by decomposing carcinogenic substances in the body, killing cancer cells, blocking nutrient source of tumor cells, inhibiting cancer cell growth, and could also reduce the incidence of prostate cancer, lung cancer, colon cancer and rectal cancer.<sup>[8-10]</sup> It has been manufactured and used to treat cancer in America, Germany, Italy, Japan, Philippines and other 20 countries. It can also ameliorate the symptoms of patients in advanced stage of cancer, and prolong their survival period. In order to provide references for the further investigations of amygdalin and new antitumor drug development, advances in studies of antitumor activities of amygdalin are reviewed in this paper.

## THE PHARMACOLOGICAL ACTIVITY OF AMYGDALIN

Amygdalin is the effective component of the traditional Chinese medicine (TCM) in bitter almond, which has been studying on for nearly two hundred years. As early as in 1803, Schrader found this substance in the study of bitter almond ingredients. Until 1830, Robiquet separated amygdalin from the bitter almond, which has always been used as auxiliary medicine of cough expectorant agent and cancer therapy.<sup>[11,12]</sup>

### Antitussive and antiasthmatic effects

After oral administration, amygdalin decomposed into hydrocyanic acid and benzaldehyde;

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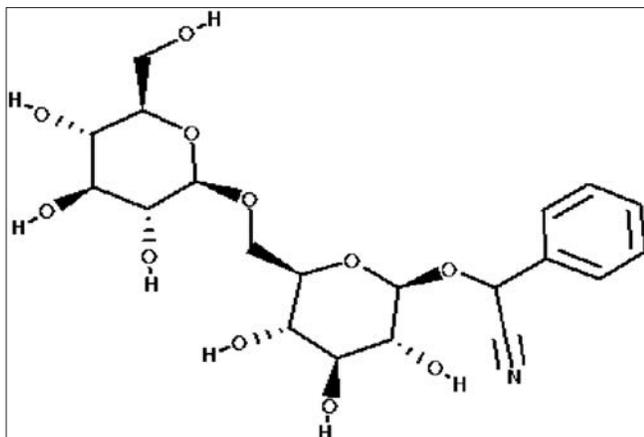
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**Figure 1:** Chemical structure of amygdalin

hydrocyanic acid could inhibit the respiratory center to a certain level, which could calm down the respiratory movement and finally achieve the antitussive and antiasthmatic effects. Amygdalin can promote the synthesis of pulmonary surfactant in animal experimental model of respiratory distress syndrome and ameliorate the disease.<sup>[13,14]</sup>

#### The effects on the digestive system

Benzaldehyde is another component that is decomposed by amygdalin through enzyme decomposition. It can inhibit the activity of pepsin and affect the digestive function. Administration of pepsin hydrolysate of almond water-solution at a dose of 500 mg/kg on CCl<sub>4</sub> treated rats, which found that it could inhibit the level of AST, ALT and increase hydroxyproline content, inhibiting the extension of euglobulinlysis time. In pathology, the soluble pepsin hydrolysate of almond water can inhibit the proliferation of connective tissue of rat liver, but could not inhibit D2 D-galactosamine induced the increase of rats' AST, ALT level. In addition, it is reported that amygdalin has a good therapeutic effects on rats with chronic gastritis and chronic atrophic gastritis.<sup>[15-17]</sup>

#### Analgesic effect

The mouse hot plate and acetic acid-induced writhing test confirmed that amygdalin has analgesic effects and no tolerance; mice without tail-erecting response and nalorphine induced jump response after treated with amygdalin.<sup>[12,18]</sup> It is demonstrated that amygdalin isolated from *Prunus armeniaca* can alleviate formalin-induced pain in rats in a dose-dependent manner with dose range less than 1 mg/kg.<sup>[19]</sup> The mechanism may involve with inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ), as well as c-Fos.<sup>[19,20]</sup> Moreover, in mouse BV2 microglial cells, amygdalin produced antiinflammatory and analgesic effects probably by inhibiting prostaglandins E2 and nitric oxide synthesis through suppressing lipopolysaccharide (LPS) induced expression of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS) on mRNA levels.<sup>[21,22]</sup>

#### Promoting apoptosis of human renal fibroblast

Amygdalin enhanced the activity of type I collagenase that secreted by the human kidney fibroblasts (KFB) within a certain concentration and action time, inhibiting the expression of type I collagen and KFB cell proliferation, promoting apoptosis of KFB cells.<sup>[23]</sup>

#### Improving the immune function of organism

Amygdalin can significantly increase polyhydroxyalkanoates (PHA) induced human peripheral blood T lymphocyte proliferation; and can promote peripheral blood lymphocytes stimulated by PHA secrete IL-2 and IFN- $\gamma$ , and then inhibit the secretion of TGF- $\beta$ 1, therefore enhance immune function.<sup>[24]</sup> Amygdalin play a positive role in the expression of regulatory T cells in the treatment of atherosclerosis, and can also expand the lumen area, reduce aortic plaque coverage.<sup>[25,26]</sup>

#### Other effects

Amygdalin can specifically inhibit the alloxan induced hyperglycemia, the effective intensity was related to the drug concentration in blood.<sup>[27]</sup> Research has shown that amygdalin has therapeutic effect on experimental gastric ulcer. Amygdalin inhibits angiogenesis in the cultured endothelial cells of diabetic rats.<sup>[6]</sup>

#### The toxicity of amygdalin

The acute toxicity experiments of amygdalin has proved that the toxicity of oral administration route is far greater than the intravenous route. The mean lethal dose (LD50) of amygdalin in rats was reported to be 880 mg/kg body weight (BW) by oral administration.<sup>[28,29]</sup> The LD50 of intravenous injection in mice are 25 g/kg, while intraperitoneal injection are 8 g/kg. The maximum tolerance dose of intravenous and intramuscular injection of amygdalin in mice, rabbits, dogs are 3 g/kg, 0.075 g/kg orally respectively;<sup>[30,31]</sup> human intravenous injection are 5 g (approximately 0.07 g/kg). Out of 10 mice injected intravenously with 500 mg/kg eight died and two survived. Research shows that the main reason is that the amygdalin was hydrolyzed by intestinal microbial after oral administration, producing more hydrocyanic acid.<sup>[32]</sup> In the mice treated by inhibiting the intestinal microbial growth, the stomach administration of 300 mg/kg also has no death phenomenon; while in the untreated mice, the mortality increased by 60% at the same dose.<sup>[32-36]</sup> Human can present systemic toxicity after oral administration of amygdalin 4 g per day, lasted for half a month or intravenous injection of a month. Moreover, the digestive system toxicity response is more common, with changes of atrial premature beats and ECG T wave. The toxicity response above can disappear after drug withdrawal. If the dose is reduced to daily oral doses of 0.6 ~ 1g, it can avoid toxicity.<sup>[32-38]</sup>

#### The anti-tumor effect of amygdalin

Amygdalin is one of the most commonly used alternative drug in the treatment of tumor in the last 40 years. Amygdalin has many nicknames, including: vitamin B17, nitriloxide, mandelonitrile,

laetrile, etc.<sup>[39]</sup> Although laetrile and amygdalin can both represent amygdalin, they are different substances. Natural amygdalin exists as a right-handed structure (R-amygdalin), which is the active form. Laetrile is the acronym of laevorotatory and mandelonitrile.<sup>[39,40]</sup> Amygdalin which has been applied for a USP (United States patent) is the semi synthetic derivatives, the structure is D-mandelonitrile- $\beta$ -glucose, however it is different with Mexico made amygdalin (D-mandelonitrile- $\beta$ -gentiobioside) in structure.<sup>[11,41]</sup>

Amygdalin was separated and purified first in 1837 by two chemists—Robiquet and Boutron, and was named as emulsion by Liebig.<sup>[42,43]</sup> A Russian doctor first tried it in the treatment of cancer in 1845. In America, amygdalin was first used to treat cancer during 1820s. In 1850s, innocuous intravenous amygdalin, called Laetrile, was registered as a patent. USA National Cancer Institute (NCI) analysis shows that, Mexico produced oral and intravenous forms of amygdalin do not conform to the American drug production standards, and other components were detected.<sup>[44]</sup> In spite of this, many American are still using amygdalin produced in Mexico. In view of this situation, USA NCI conducted clinical studies on its effectiveness. In 22 cases of drug treated patients, only 6 cases had good effects against cancer, it does not good enough to support the antitumor effects of amygdalin.<sup>[45]</sup> American food and drug administration (FDA) prescribed amygdalin (Laetrile) products as toxic in 1979, which cannot be used as drug. Amygdalin was banned in America.<sup>[46,47]</sup> In 1980, 23 states of USA restored application of amygdalin in the treatment of advanced cancer patients.<sup>[48]</sup> Unfortunately, American FDA approved NCI two clinical trials of amygdalin, the results could not confirmed the effectiveness of amygdalin. In 1987, the imports of amygdalin were banned in USA, afterwards amygdalin was banned in USA and Europe.<sup>[48]</sup> In the UK, the drug can produce cyanide and has been listed as a prescription drug, which can be used under the supervision of a doctor.<sup>[49]</sup> Thus, as an antitumor drug, of the mass production and application of amygdalin is mainly in Mexico.<sup>[50]</sup>

Amygdalin is mainly as an alternative therapy for traditional cancer treatment, or combined with other nonconventional treatments, such as metabolic therapy, urine therapy, dietotherapy, intake of fruit seeds, intravenous injection of  $\beta$ -glucosidases and so on.<sup>[51-53]</sup>  $\beta$ -glucosidases enzyme was found from the intestinal bacteria,<sup>[32]</sup> it also can be found in edible plants, with function of decomposing amygdalin into benzaldehyde, glucose and hydrocyanic acid.<sup>[54]</sup> Amygdalin exists in the related products of amygdalin and Laetrile, is the active component of drugs.<sup>[55]</sup>

Many experiment results supported that, amygdalin has antitumor activity.<sup>[39,56,57]</sup> Amygdalin and other cyanogenic sugar, are also considered to be a potential alternative antitumor drug.<sup>[57,58]</sup>

Recently, some advances had been made on the antitumor

mechanism of amygdalin. Kwon *et al.*, confirmed that amygdalin can induce apoptosis in human promyelocytic leukemia (HL-60) cells;<sup>[59]</sup> Park *et al.*, have shown that amygdalin inhibited the proliferation of human colon cancer SNU-C4 cell, and the mechanism is the inhibition of expression of cell cycle related genes;<sup>[9]</sup> Chang *et al.*, identified that amygdalin can induce apoptosis in prostate cancer DU145 and LNCaP cells by regulating the expression of Bax and of Bcl-2.<sup>[8,11,60]</sup> Chen, Y. *et al.*,<sup>[10]</sup> found that amygdalin can inhibit the survival rate of HeLa cells, in a concentration dependent manner. Amygdalin can induce apoptosis of HeLa cells mediated by endogenous mitochondrial pathway. Amygdalin could also inhibit the growth of HeLa cell in nude mice bearing tumors through inducing tumor cell apoptosis. The detection results of human whole genome U133 microarray showed that 573 genes of HeLa cells had differential expression in the amygdalin treated group, compared with the control group, JNK/c-Jun pathway is involved in the process of amygdalin induced apoptosis in HeLa cells. Nevertheless, the antitumor mechanism of amygdalin is not completely clear. Clinical trials and large retrospective studies showed that bitter almond had no stable antitumor effect, most importantly is the existence of some adverse reactions after large dose application, such as gastrointestinal tract reaction and headache.<sup>[61-67]</sup> But in view of the quantity and quality of clinical data are limited, so far clinical studies have no paired and reliable design, so it is necessary to conduct more carefully designed controlled clinical trials for bitter almond, and prove its effect *in vivo*.<sup>[60]</sup>

## CONCLUSION

There has been done a lot of work in the analysis of amygdalin, the analysis and detection methods of amygdalin were more perfect and mature; and a large number of studies have shown that amygdalin plays a supporting role in the treatment of cancer, diabetes, atherosclerosis, immune suppression, leprosy and other diseases. This paper reviews recent progression of amygdalin in cancer research. Amygdalin has a clear pharmacological activity, but there are still little in-depth research on the pharmacological mechanism of the compound, so it has an important application value to systematically investigate the mechanism of amygdalin pharmacological activity and develop antitumor drugs.

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