Review Article

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

Zuoqing Song, Xiaohong Xu[1]

Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, [1]Department of Nursing, College of Nursing, Tianjin Medical University, Tianjin, China

For correspondence:
Dr. Xiaohong Xu, College of Nursing, Tianjin Medical University, Tianjin 300070, China.
E-mail: szqing5852210@163.com

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-mand elonitrile-β-D-glucoside-6-β-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.[1,2] 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.[3] 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.[4-7] It has been used for the treatment of asthma, bronchitis, emphysema, leprosy, colorectal cancer and vitiligo.[5] 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.[8] Therefore the anti-tumor effect of amygdalin is one of the hots 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.[8-10] 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.[11,12]

Antitussive and antiasthmatic effects

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

Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.139743

PMID: ***

Quick Response Code:

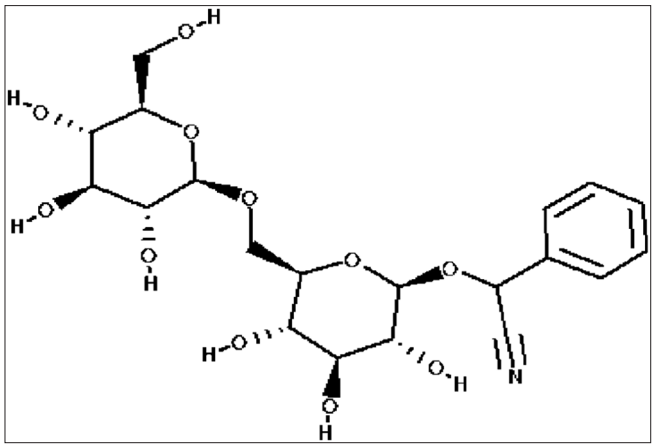

Figure 1: Chemical structure of amygdalin

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.[13,14]

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_4 treated rats, which found that it could inhibit the level of AST, ALT and increase hydroxyproline content, inhibiting the extention 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.[15-17]

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.[12,18] 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.[19] The mechanism may involve with inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), as well as c-Fos.[19,20] 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.[21,22]

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.[23]

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-γ, and then inhibit the secretion of TGF-β1, therefore enhance immune function.[24] 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.[25,26]

Other effects

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

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.[28,29] 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;[30,31] human intravenous injection are 5 g (approximately 0.07 g/kg). Out of 10 mice injected intravenouly 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.[32] 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.[32-36] 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.[32-38]

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, nitriloside, mandelonitrile,

laetrile, etc.[39] 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.[39,40] Amygdalin which has been applied for a USP (United States patent) is the semi synthetic derivatives, the structure is D-mandelonitrile-β-glucose, however it is different with Mexico made amygdalin (D-mandelonitrile-β-gentiobioside) in structure.[11,41]

Amygdalin was separated and purified first in 1837 by two chemists–Robiquet and Boutron, and was named as emulsion by Liebig.[42,43] 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.[44] 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.[45] 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.[46,47] In 1980, 23 states of USA restored application of amygdalin in the treatment of advanced cancer patients.[48] 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.[48] 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.[49] Thus, as an antitumor drug, of the mass production and application of amygdalin is mainly in Mexico.[50]

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 β-glucosidases and so on.[51-53] β-glucosidases enzyme was found from the intestinal bacteria,[32] it also can be found in edible plants, with function of decomposing amygdalin into benzaldehyde, glucose and hydrocyanic acid.[54] Amygdalin exists in the related products of amygdalin and Laetrile, is the active component of drugs.[55]

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

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;[59] 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;[9] 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.[8,11,60] Chen, Y. *et al*.,[10] 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 inducting 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.[61-67] 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*.[60]

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.

ACKNOWLEDGEMENTS

This work was partly supported by the grants from Tianjin Municipal Health Burea Fund (No. 2011KZ106), Tianjin Municipal Education Commission Fund (No. 20120127), and Tianjin Municipal Science and Technology Commission Fund (No. 14JCYBJC28400).

REFERENCES

1. Holzbecher MD, Moss MA, Ellenberger HA. The cyanide content of laetrile preparations, apricot, peach and apple seeds. J Toxicol Clin Toxicol 1984;22:341-7.
2. Santos Pimenta LP, Schilthuizen M, Verpoorte R, Choi YH. Quantitative analysis of amygdalin and prunasin in Prunus serotina Ehrh. using (1)

H-NMR spectroscopy. Phytochem Anal 2014;25:122-6.
3. Suchard JR, Wallace KL, Gerkin RD. Acute cyanide toxicity caused by apricot kernel ingestion. Ann Emerg Med 1998;32:742-4.
4. Du HK, Song FC, Zhou X, Li H, Zhang JP. Effect of amygdalin on serum proteinic biomarker in pulmonary fibrosis of bleomycin-induced rat. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2010;28:260-3.
5. Chang HK, Yang HY, Lee TH, Shin MC, Lee MH, Shin MS, *et al*. Armeniacae semen extract suppresses lipopolysaccharide-induced expressions of cyclooxygenase [correction of cycloosygenase]-2 and inducible nitric oxide synthase in mouse BV2 microglial cells. Biol Pharm Bull 2005;28:449-54.
6. Mirmiranpour H, Khaghani S, Zandieh A, Khalilzadeh OO, Gerayesh-Nejad S, Morteza A, *et al*. Amygdalin inhibits angiogenesis in the cultured endothelial cells of diabetic rats. Indian J Pathol Microbiol 2012;55:211-4.
7. Chan TY. A probable case of amygdalin-induced peripheral neuropathy in a vegetarian with vitamin B12 deficiency. Ther Drug Monit 2006;28:140-1.
8. Chang HK, Shin MS, Yang HY, Lee JW, Kim YS, Lee MH, *et al*. Amygdalin induces apoptosis through regulation of Bax and Bcl-2 expressions in human DU145 and LNCaP prostate cancer cells. Biol Pharm Bull 2006;29:1597-602.
9. Park HJ, Yoon SH, Han LS, Zheng LT, Jung KH, Uhm YK, *et al*. Amygdalin inhibits genes related to cell cycle in SNU-C4 human colon cancer cells. World J Gastroenterol 2005;11:5156-61.
10. Chen Y, Ma J, Wang F, Hu J, Cui A, Wei C, *et al*. Amygdalin induces apoptosis in human cervical cancer cell line HeLa cells. Immunopharmacol Immunotoxicol 2013;35:43-51.
11. Milazzo S, Ernst E, Lejeune S, Boehm K, Horneber M. Laetrile treatment for cancer. Cochrane Database Syst Rev 2011:CD005476.
12. Holland JC. Why patients seek unproven cancer remedies: A psychological perspective. CA Cancer J Clin 1982;32:10-4.
13. Chang LW, Zhu HP, Li WB, Liu HC, Zhang QS, Chen HB. Protective effects of amygdalin on hyperoxia-exposed type II alveolar epithelial cells isolated from premature rat lungs *in vitro*. Zhonghua Er Ke Za Zhi 2005;43:118-23.
14. Do JS, Hwang JK, Seo HJ, Woo WH, Nam SY. Antiasthmatic activity and selective inhibition of type 2 helper T cell response by aqueous extract of semen armeniacae amarum. Immunopharmacol Immunotoxicol 2006;28:213-25.
15. Wei Y, Xie Q, Ito Y. Preparative separation of axifolin-3-glucoside, hyperoside and amygdalin from plant extracts by high-speed countercurrent chromatography. J Liq Chromatogr Relat Technol 2009;32:1010-22.
16. Xin GX, Yang MY. Progress of natural amygdalin research. Chin Tradit Patent Med 2003;25:1007-9.
17. Shim SM, Kwon H. Metabolites of amygdalin under simulated human digestive fluids. Int J Food Sci Nutr 2010;61:770-9.
18. Zhu YP, Su ZW, Li CH. Analgesic effect and no physical dependence of amygdalin. Zhongguo Zhong Yao Za Zhi 1994;19:105-7, 128.
19. Hwang HJ, Kim P, Kim CJ, Lee HJ, Shim I, Yin CS, *et al*. Antinociceptive effect of amygdalin isolated from Prunus armeniaca on formalin-induced pain in rats. Biol Pharm Bull 2008;31:1559-64.
20. Hwang HJ, Lee HJ, Kim CJ, Shim I, Hahm DH. Inhibitory effect of amygdalin on lipopolysaccharide-inducible TNF-alpha and IL-1beta mRNA expression and carrageenan-induced rat arthritis. J Microbiol Biotechnol 2008;8:1641-7.
21. Yang HY, Chang HK, Lee JW, Kim YS, Kim H, Lee MH, *et al*. Amygdalin suppresses lipopolysaccharide-induced expressions of cyclooxygenase-2 and inducible nitric oxide synthase in mouse BV2 microglial cells. Neurol Res 2007;29 Suppl 1:S59-64.
22. Paoletti I, De Gregorio V, Baroni A, Tufano MA, Donnarumma G, Perez JJ. Amygdalin analogues inhibit IFN-gamma signalling and reduce the inflammatory response in human epidermal keratinocytes. Inflammation 2013;36:1316-26.
23. Guo J, Wu W, Sheng M, Yang S, Tan J. Amygdalin inhibits renal fibrosis in chronic kidney disease. Mol Med Rep 2013;7:1453-7.
24. Baroni A, Paoletti I, Greco R, Satriano RA, Ruocco E, Tufano MA, *et al*. Immunomodulatory effects of a set of amygdalin analogues on human keratinocyte cells. Exp Dermatol 2005;14:854-9.
25. Jiagang D, Li C, Wang H, Hao E, Du Z, Bao C, *et al*. Amygdalin mediates relieved atherosclerosis in apolipoprotein E deficient mice through the induction of regulatory T cells. Biochem Biophys Res Commun 2011;411:523-9.
26. Perez JJ. Amygdalin analogs for the treatment of psoriasis. Future Med Chem 2013;5:799-808.
27. Heikkila RE, Cabbat FS. The prevention of alloxan-induced diabetes by amygdalin. Life Sci 1980;27:659-62.
28. Adewusi SR, Oke OL. On the metabolism of amygdalin. 1. The LD50 and biochemical changes in rats. Can J Physiol Pharmacol 1985;63:1080-3.
29. Park JH, Seo BI, Cho SY, Park KR, Choi SH, Han CK, *et al*. Single oral dose toxicity study of prebrewed armeniacae semen in rats. Toxicological Res 2013;29:91-8.
30. Zhang GM, Jin BQ. Pharmacokinetics of amygdalin in rabbits. Zhongguo Yao Li Xue Bao 1986;7:460-2.
31. Rauws AG, Olling M, Timmerman A. The pharmacokinetics of prunasin, a metabolite of amygdalin. J Toxicol Clin Toxicol 1982;19:851-6.
32. Carter JH, McLafferty MA, Goldman P. Role of the gastrointestinal microflora in amygdalin (laetrile)-induced cyanide toxicity. Biochem Pharmacol 1980;29:301-4.
33. Khandekar JD, Edelman H. Studies of amygdalin (laetrile) toxicity in rodents. JAMA 1979;242:169-71.
34. Stock CC. Amygdalin (Laetrile) toxicity in rodents. JAMA 1979;242:2287.
35. Khandekar JD. Amygdalin (laetrile) toxicity in rodents. JAMA 1980;243:2396.
36. Newton GW, Schmidt ES, Lewis JP, Conn E, Lawrence R. Amygdalin toxicity studies in rats predict chronic cyanide poisoning in humans. West J Med 1981;134:97-103.
37. Bromley J, Hughes BG, Leong DC, Buckley NA. Life-threatening interaction between complementary medicines: Cyanide toxicity following ingestion of amygdalin and vitamin C. Ann Pharmacother 2005;39:1566-9.
38. O'Brien B, Quigg C, Leong T. Severe cyanide toxicity from 'vitamin supplements' Eur J Emerg Med 2005;12:257-8.
39. Fukuda T, Ito H, Mukainaka T, Tokuda H, Nishino H, Yoshida T. Anti-tumor promoting effect of glycosides from Prunus persica seeds. Biol Pharm Bull 2003;26:271-3.
40. Howard-Ruben J, Miller NJ. Unproven methods of cancer management. Part II: Current trends and implications for patient care. Oncol Nurs Forum 1984;11:67-73.
41. Fenselau C, Pallante S, Batzinger RP, Benson WR, Barron RP, Sheinin EB, *et al*. Mandelonitrile beta-glucuronide: Synthesis and characterization. Science 1977;198:625-7.
42. Laetrile--its current status. Medical Times 1980;108:36-45.
43. Dorr RT, Paxinos J. The current status of laetrile. Ann Intern Med 1978;89:389-97.
44. Davignon JP, Trissel LA, Kleinman LM. Pharmaceutical assessment of amygdalin (Laetrile) products. Cancer Treat Rep 1978;62:99-104.
45. Ellison NM, Byar DP, Newell GR. Special report on Laetrile: The NCI Laetrile Review. Results of the National Cancer Institute's retrospective Laetrile analysis. N Engl J Med 1978;299:549-52.
46. Bitting TH. Drugs--Federal Drug Administration ban on Laetrile treatments for terminally ill cancer patients is arbitrary and capricious. Tulsa Law J 1978;14:222-5.
47. Shishkovsky KR. Administrative law. Laetrile and other drugs to be used by the terminally ill are not exempt from the safety and effectiveness requirements of the Federal Food, Drug, and Cosmetic Act of 1938. J Urban Law 1980;57:364-88.
48. Curran WJ. Law-medicine notes. Laetrile for the terminally ill:

Supreme Court stops the nonsense. N Engl J Med 1980;302:619-21.
49. Bolarinwa IF, Orfila C, Morgan MR. Amygdalin content of seeds, kernels and food products commercially-available in the UK. Food Chem 2014;152:133-9.
50. Questionable cancer practices in Tijuana and other Mexican border clinics. CA Cancer J Clin 1991;41:310-9.
51. Moertel CG, Fleming TR, Rubin J, Kvols LK, Sarna G, Koch R, *et al*. A clinical trial of amygdalin (Laetrile) in the treatment of human cancer. N Engl J Med 1982;306:201-6.
52. Liao ZG, Ling Y, Zhong Y, Ping QN. The simultaneous determination of laetrile, paeoniflorin and paeonol in Jingzhi Guizhi Fuling capsule by HPLC. Zhongguo Zhong Yao Za Zhi 2005;30:1252-4.
53. Zhou C, Qian L, Ma H, Yu X, Zhang Y, Qu W, *et al*. Enhancement of amygdalin activated with beta-D-glucosidase on HepG2 cells proliferation and apoptosis. Carbohydr Polym 2012;90:516-23.
54. Newmark J, Brady RO, Grimley PM, Gal AE, Waller SG, Thistlethwaite JR. Amygdalin (Laetrile) and prunasin beta-glucosidases: Distribution in germ-free rat and in human tumor tissue. Proc Natl Acad Sci U S A 1981;78:6513-6.
55. Miller KW, Anderson JL, Stoewsand GS. Amygdalin metabolism and effect on reproduction of rats fed apricot kernels. J Toxicol Environ Health 1981;7:457-67.
56. Biaglow JE, Durand RE. The enhanced radiation response of an *in vitro* tumour model by cyanide released from hydrolysed amygdalin. Int J Radiat Biol Relat Stud Phys Chem Med 1978;33:397-401.
57. Kousparou CA, Epenetos AA, Deonarain MP. Antibody-guided enzyme therapy of cancer producing cyanide results in necrosis of targeted cells. Int J Cancer 2002;99:138-48.
58. Syrigos KN, Rowlinson-Busza G, Epenetos AA. *In vitro* cytotoxicity following specific activation of amygdalin by beta-glucosidase conjugated to a bladder cancer-associated monoclonal antibody. Int J Cancer 1998;78:712-9.
59. Kwon HY, Hong SP, Hahn DH, Kim JH. Apoptosis induction of Persicae Semen extract in human promyelocytic leukemia (HL-60) cells. Arch Pharm Res 2003;26:157-61.
60. Milazzo S, Lejeune S, Ernst E: Laetrile for cancer: A systematic review of the clinical evidence. Supportive Care Cancer 2007;15:583-95.
61. Unproven methods of cancer management. Laetrile. CA Cancer J Clin 1991;41:187-92.
62. Shils ME, Hermann MG. Unproved dietary claims in the treatment of patients with cancer. Bull N Y Acad Med 1982;53:323-40.
63. Greenberg DM. The case against laetrile: The fraudulent cancer remedy. Cancer 1980;45:799-807.
64. Herbert V. Laetrile: The cult of cyanide. Promoting poison for profit. Am J Clin Nutr 1979;32:1121-58.
65. Barwina M, Wiergowski M, Sein Anand J. Accidental poisoning with peach seeds used as anticancer therapy--report of two cases. Przegl Lek 2013;70:687-9.
66. Yang D, Qiu M, Zou LQ, Zhang W, Jiang Y, Zhang DY, Yan X. The role of palliative chemotherapy for terminally ill patients with advanced NSCLC. Thorac Cancer 2013;4:153-60.
67. Karabulutlu EY. Coping with stress of family caregivers of cancer patients in Turkey. Asia Pac J Oncol Nurs 2014;1:55-60.

Cite this article as: Song Z, Xu X. Advanced research on anti-tumor effects of amygdalin. J Can Res Ther 2014;10:3-7.

Source of Support: Nil, **Conflict of Interest:** None declared.