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A REVIEW

AMYGDALIN AND ITS EFFECTS ON ANIMAL CELLS

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ABSTRACT

Amygdalin is a natural compound whose anticancer, anti-inflammatory activity and other medicinal benefits have been known for many years. It has been isolated in 1830 by the French chemists Robiquet and Boutron-Charlard from kernels of the bitter almond (*Prunus amygdalus*). It is a major component of the seeds of prunasin family plants, such as apricots, almonds, peaches, apples, and other rosaceous plants. Amygdalin is composed of two molecules of glucose, one of benzaldehyde, which induces an analgesic action, and one of hydrocyanic acid, which is an anti-neoplastic compound. It has been used as a traditional drug because of its wide range of medicinal benefits. Amygdalin can be used in medicine for preventing and treating migraine, hypertension, chronic inflammation, and other reaction source diseases. This review is focused on the effects of amygdalin on the animal system.

Keywords: amygdalin, animal cells cancer, reproduction, proliferation, apoptosis

INTRODUCTION

Characteristic

Amygdalin is a cyanogenic glucoside initially isolated from the seeds of bitter almonds (*Prunus dulcis*) (**Chwalek and Plé, 2004**). It is a major component of the seeds of

prunasin family plants, such as apricots, almonds, peaches, apples, and other rosaceous plants (**Fukuta *et al.*, 2003**). Its oldest known use was by the ancient Egyptians as a poison for executing capital punishment: "penalty of the peach". It has been isolated in 1830 by the French chemists Robiquet and Boutron-Charlard from kernels of the bitter almond (*Prunus amygdalus*) and has been thoroughly investigated in 1837 by Liebig and Wöhler. Its detailed chemical structure was at last established by the carbohydrate chemists Haworth and Wylam in 1923 (**Rauws *et al.*, 1982**).

Amygdalin (D-mandelonitrile-β-D-gentiobioside, Fig. 1A), $C_{20}H_{27}NO_{11}$, is composed of two molecules of glucose, one of benzaldehyde, which induces an analgesic action, and one of hydrocyanic acid, which is an anti-neoplastic compound (**Chang *et al.*, 2006**).

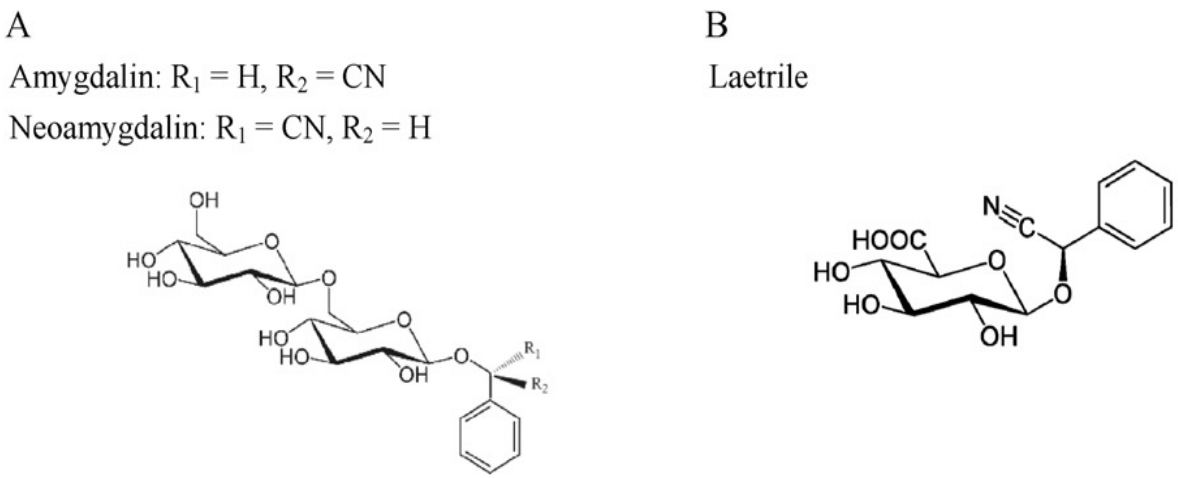

Figure 1 (A) Molecular structure of amygdalin (D-mandelonitrile-β-D-gentiobioside, $C_{20}H_{27}NO_{11}$). (B) Molecular structure of laetrile (cyanophenylmethyl-β-D-glucopyranosiduronic acid, $C_{14}H_{15}NO_7$) (**Zhou *et al.*, 2012**)

Amygdalin is sometimes confused with laevomandelonitrile (Cyanophenylmethyl-β-D-glucopyranosiduronic acid, Fig. 1B), $C_{14}H_{15}NO_7$, which is commonly known as laetrile. However, amygdalin and laetrile are different chemical compounds (**Andrew *et al.*, 1980; Du *et al.*, 2005**).

Metabolism

Beta-glucosidase, one of the enzymes that catalyzes the release of cyanide from amygdalin, is present in the human small intestine and is also found in a variety of common foods (**Strugala *et al*., 1995; Deng *et al*., 2002**). *In vivo* the enzyme complex emulsin containing the enzymes β-D-glucosidase, benzocyanase, and others, degrades the amygdalin into four components: hydrocyanic acid, benzaldehyde, prunasin, and mandelonitrile, which are absorbed into the lymph and portal circulations (**Chang and Zhang, 2012**).

The enzymatic breakdown of amygdalin occurs most rapidly in alkaline conditions. The β-glucosidase may be deactivated in the acid environment of the stomach but can then be partially reactivated in the alkaline environment of the gut (**JECFA, 1993**). Cyanogenic glycosides can also be hydrolysed by gut flora. Amygdalin is metabolized by the body to produce cyanide, a very rapid poison which impairs cellular respiration leading to a cascade of events culminating in death (**Ballantyne and Marrs, 1987**).

Effects on the animal organism

The effects of natural substances on animal organism concentrated on the reproductive system (**Kolesarova *et al*., 2012a; 2012b; 2011**; **Kádasi *et al*., 2012; Tanyildizy and Bozkurt, 2004; Yasui *et al*., 2003; Randel *et al*., 1992;**) were studied in the previous studies. Natural plant origin products like amygdalin are still a major part of traditional medicine (**Nabavizadeh *et al*., 2011**). It has been used as a traditional drug because of its wide range of medicinal benefits, including curing or preventing cancer, relieving fever, suppressing cough, and quenching thirst (**Zhou *et al*., 2012**).

Amygdalin was used as an anticancer agent in Russia as early as 1845, with positive results reported for the first patient treated (**Moss, 1996**). In the late 1970s and early 1980s, amygdalin was reported to selectively kill cancer cells at the tumor site without systemic toxicity and to effectively relieve pain in cancer patients (**Zhou *et al*., 2012**). Various rodent cancers (osteogenic sarcoma, melanoma, carcinosarcoma, lungcarcinoma, and leukemia) were transplanted into rats and mice. The animals were treated with intraperitoneal injections of amygdalin, with or without the enzyme beta-glucosidase. None of the solid tumors or leukemias investigated responded to amygdalin at any dose tested. No statistically significant increase in animal survival was observed in any of the treatment groups (**Wodinsky and Swiniarski, 1975; Laster and Schabel, 1975**).

However, positive results were obtained in other studies. Amygdalin enhanced the antitumor activity of a combination of enzymes and vitamin A in mice bearing spontaneous mammary adenocarcinomas. The amygdalin was given by intramuscular injection, the vitamin A was administered orally through a feeding tube, and the enzymes were injected into and around tumor masses. No anticancer activity was observed when amygdalin was given alone (**Manner *et al.*, 1978**). White blood cells and prostate cancer specimens were used to investigate the potential of amygdalin to stimulate the immune system. Amygdalin caused a statistically significant increase in the ability of a patient's white blood cells to adhere to his own prostate cancer cells, suggesting some immune system boosting potential for amygdalin (**Bhatti *et al.*, 1981**). The ability of amygdalin and beta-glucosidase to indirectly sensitize the hypoxic (oxygen-starved) cells at the center of a tumor to the lethal effects of gamma irradiation was investigated. Cells at the periphery (outer edge) of a tumor are more sensitive to gamma irradiation because they are not oxygen-deprived. Presumably, cyanide uptake by interior tumor cells is less than that of cells located at a tumor's periphery. The investigators found that amygdalin and beta-glucosidase could act as indirect radiation sensitizers of hypoxic tumor cells (**Biaglow and Durand, 1978**). Cultured human bladder cancer cells were treated with amygdalin alone or a combination of amygdalin and an antibody that was coupled (chemically) to beta-glucosidase. The target for this antibody was the glycoprotein (a protein with sugar molecules attached) MUC1. In this study, amygdalin alone was not very effective in killing the bladder cancer cells, but its cell-killing ability was 36 times greater in the presence of the antibody-enzyme complex. (**Syrigos *et al.*, 1998**). Amygdalin induced DNA damage, involved in cell cycle on SNU-C4 human colon cancer cells and amygdalin might be used for therapeutic anticancer drug (**Park *et al.*, 2005**). However, the Food and Drug Administration (FDA) has not approved amygdalin as a cancer treatment owing to insufficient clinical evidence of its efficacy and potential toxicity. Despite the failure of clinical tests to demonstrate the anticancer effects of amygdalin in the U.S.A. and in Europe, amygdalin continues to be manufactured and administered as an anticancer therapy in northern Europe and Mexico (**Chang *et al.*,2006; Kwon *et al.*, 2010**).

Besides the antitumor activity, amygdalin has also been used for the treatment of asthma, bronchitis, emphysema, leprosy and diabetes (**Zhou *et al.*, 2012**). It is also decomposed by the action of β-D-glucosidase to yield hydrocyanic acid which stimulates the respiratory center reflexively and produces a kind of antitussive and antiasthmatic effects (**Badr and Tawfik, 2010; Lv *et al.*, 2005**). Amygdalin can be used in medicine for preventing and treating migraine, hypertension, chronic inflammation, and other reaction

source diseases (**Yan *et al*., 2006**). In addition, it can be used as a cerebral function improver that is effective as a therapeutic agent for cerebrovascular lesions such as psychogenic symptoms, nerve symptoms, subjective symptoms, and daily life activity disorder (**Hiromi, 1995**).

Amygdalin significantly inhibited sperm hyaluronidase activity. The inhibition of hyaluronidase activity can cause a drop in the fertilization ability of bull spermatozoa due to the prevention of acrosomal reaction. However, amygdalin did not produce any morphological abnormality in bull spermatozoa. The inhibition of sperm hyaluronidase activity and spermatozoa motility showed that these compound have deleterious effects on bull sperm *in vitro* (**Tanyildizy and Bozkurt, 2004**). Amygdalin is one of main pharmacological components of crude ingredients of *Keishi-bukuryo-gan,* Japanese herbal medicine (**Yasui *et al*., 2003**). It has been used for induction of ovulation in women suffering from infertility (**Igarashi, 1988**). *Keishi-bukuryo-gan* and its crude ingredients affected steroidogenesis in pre-ovulatory follicles (**Usuki, 1987, 1990, 1991**) and the *corpus luteum* (**Usuki, 1986, 1988**) in the rat ovary *in vivo* and *in vitro*.

Mechanism of the effect

Recent data indicated that amygdalin reduced proliferation potential, decreased mitochondrial activity of cervical cancer cells, accumulated cells in G1 phase and lead to their death (**Jarocha and Majka, 2011**). Amygdalin induces apoptotic cell death by caspase-3 activation through the down-regulation of anti-apoptotic Bcl-2 protein and the up-regulation of pro-apoptotic Bax protein in DU145 and LNCaP prostate cancer cells (**Chang *et al*., 2006**).

Previous studies on amygdalin have focused on its purification, toxicity related to the release of cyanide, anti-tumor mechanism, and identification of its metabolites in plasma or herbs, and its pharmacological effect on cancers (**Rauws *et al*., 1982**).

CONCLUSION

This review suggest possible effects of amygdalin on animal cells. Besides the antitumor activity, amygdalin has also been used for the treatment of asthma, bronchitis, emphysema, leprosy and diabetes. In addition, it can be used as a cerebral function improver that is effective as a therapeutic agent for cerebrovascular lesions. On the other hand there

have been demonstrated its negative effects. There are still few studies that suggest the possible impact of amygdalin on animal reproduction system.

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