

Review Article

Amygdalin laetrile-a nascent vitamin B17: a review

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ABSTRACT

Amygdalin is also called Vitamin B17 and its semi synthetic product is laetrile. It is a natural glycoside nutrient which gained popularity due to wide availability and low cost in treating various diseases. Vitamin B17 is derived from natural food sources and can be used for cancer prevention in alternative medicine practices. This review illustrates the proposed anticancer activity and other effects of amygdalin on different body systems along with a variety of clinical trials on humans and animals with pharmacological, toxicological effects and provides a perspective for further investigation and research.

Keywords: Amygdalin, Antitumor, Beta-glucuronidase, Cyanogenic Toxicity, Laetrile, Rhodanese, Vitamin B17

INTRODUCTION

Amygdalin, also named as 'laetrile' and 'vitamin B17' was recognized over the years by the followers of natural medicine and has been proposed in research to be having anticancer effects.¹ It is one of the most controversial vitamins in the last three decades. It is a cyanogenic plant glucoside belonging to the Rosaceae family found in the pits of numerous fruits, raw nuts as apricot stones, almonds, cherries, peaches and plums. It is also found in plants, such as lima beans, clover, and sorghum.² Laetrile word is derived from the terms levorotatory and mandelonitrile.^{1,3} Laevorotary describes stereochemistry while mandelonitrile refers to its chemical identity. Amygdalin has chemical formula C₂₀H₁₀NO₁₁ and molecular weight is supposed to be 457.42 Dalton. It was used to treat asthma, bronchitis, leprosy and leukoderma in ancient period.¹ Amygdalin produces HCN which is poisonous and is decomposed by enzymes. The various pharmacological effects of laetrile include antiatherogenic, activity in renal fibrosis, pulmonary

fibrosis, immune regulation, antitumor, anti-inflammatory activities. Laetrile has been manufactured and used by over 20 countries like Japan, China, America and Italy for cure of cancer as an alternative medicine. In recent years, anti-cancerous effect of amygdalin has become an upcoming and controversial topic. Though it was encouraged for cure of cancer due to lack of sufficient clinical trials and some adverse cyanogenic effects it was not promoted by FDA fully for cancer therapy.

Amygdalin was first discovered by Schrader et al, in 1803.⁴ Laetrile is short name for levomandelonitrile and was awarded its vitamin status officially in 1952. But the systematized study of vitamin B17 started when the chemist Bohn (1802) discovered that during the distillation of the water from bitter almonds hydrocyanic acid was released. Robiquet and Boutron, French chemists in 1830 isolated a crystalline amygdalin from bitter almond. Some of the oldest civilizations from Egypt and China, described the therapeutic use of bitter almonds derivatives e.g., for the treatment of skin

tumours (Contreras, 1980).⁵ The Greeks and Romans also mentioned therapeutic properties of low doses of amygdalin extract. In 1950 it was patented as a non-toxic intravenous form and reported to be an effective compound in the treatment of cancer. More than 70,000 people were reported to have been treated with laetrile in 1978 in the United States.⁶ The US Food and Drug Administration (FDA), the American Medical Association (AMA) and the American Cancer Society (ACS) found that the efficacy of laetrile has not proven to be true. The FDA made regulations regarding the administration of laetrile therapy however; no laws were issued to include laetrile in the list of prohibited drugs.⁷

Treatment trials with laetrile in humans

Manuel Navarro (1957, 1971) treated over five hundred patients in a state with laetrile using the intravenous and oral route of administration. Some of the cancers best treated were adenocarcinoma of stomach, lungs, breast, rectum, oesophagus, lymphosarcomas, fibrosarcomas etc.⁸ Binzel PE treated cancer patients with intravenous and oral laetrile between 1974 and 1991 and published his results. Intravenous doses started upto 3 gms and worked upto 9gms. Henceforth oral laetrile 1 gm was started at bedtime.⁹ Contreras E et al (1980) remarked Laetrile as most effective for prevention of cancer. Its nontoxicity permits its use while surgery, radiation and chemotherapy. Laetrile in conjunction with vitamin A and enzymes was proved to be very effective.⁵ Schacter M et al proposed the use of cysteine along with amygdalin to reduce the cyanogenic effects of laetrile.¹⁰ Three best case series published between 1953-1962 provided convincing data supporting the use of laetrile.¹¹ But sufficient numbers of control groups were absent and positive findings were based on mere subjective improvements in health. In 1830, chemists in France first isolated Amygdalin and it was first used as a treatment for cancer in Russia in 1845. In the United States, it was used in 1920's. 22 case studies regarding use of laetrile as an alternative therapy was done by NCI, out of which 6 cases were successful. But FDA banned the use of laetrile in 1979.¹²

Chemistry of laetrile

Laetrile is a cyanogenic glycoside derived from phenylalanine. Laetrile is degraded to gentiobiose and L-mandelonitrile. Gentiobiose is further hydrolysed to glucose while L-mandelonitrile into hydrogen cyanide and benzaldehyde (13). The chemical structure of laetrile is D-mandelonitrile-β-D-glucoside-6-β-glucoside (Figure 1).^{14,15}

Preparation of amygdalin

Amygdalin is generally obtained from the cake of bitter almond after extraction of the fixed oil. Extraction is done with ethanol (95% v/v) and the resulting alcoholic extract is concentrated to a small volume under vacuum

and mixed with a large volume of ether. The desired glycoside will separate out as a crystalline product. Enzymatic hydrolysis of amygdalin gives rise to one mole each of benzaldehyde and hydrocyanic acid plus two moles of glucose (Figure 2).^{16,17}

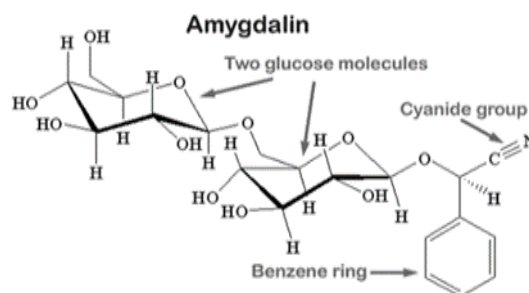


Figure 1: Structure of Amygdalin.

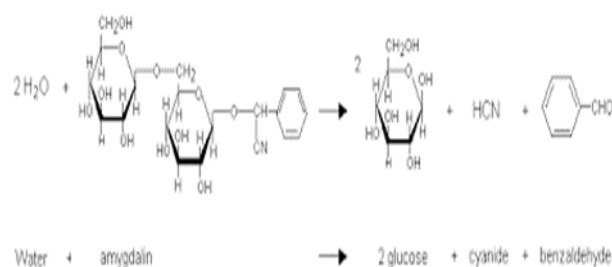


Figure 2: Conversion of Amygdalin to laetrile.

Methods of extraction

There are three methods of extraction i.e., Ultrasonic extraction by methanol, Soxhlet extraction by methanol and Reflux extraction by water containing 0.1 % citric acid is the best option.

Mechanism of action

Ernst T Krebs Jr. who gave the term vitamin B17 to laetrile in his research mentioned that Rhodanese is usually found in normal cells. Vitamin B17 consists of 2 parts glucose, 1part HCN, 1part benzaldehyde. When Rhodanese comes in contact with vitamin B17 it converts HCN and benzaldehyde into two byproducts- Thiocyanate and benzoic acid which nourishes the normal cells. Cancer cells contain the enzyme beta glucosidase. When vitamin B17 comes in contact with cancer cells vitamin B17 is broken down by beta-glucosidase into benzaldehyde and hydrocyanic acid. These two forms a toxic product and destroy cancer cells by selective toxicity.¹⁰ The transportation mechanism for laetrile in the body is zinc. Manner et al found that the cancer is treated best with a nutritional program consisting of diet, vitamins, minerals, laetrile and pancreatic enzymes.¹⁸ A study by Li Yun-long et al targeting amygdalin, cancer cells showed positive cell lysis proving HCN and beta glucosidase activities in cancer therapy (Figure 3).^{19,20}

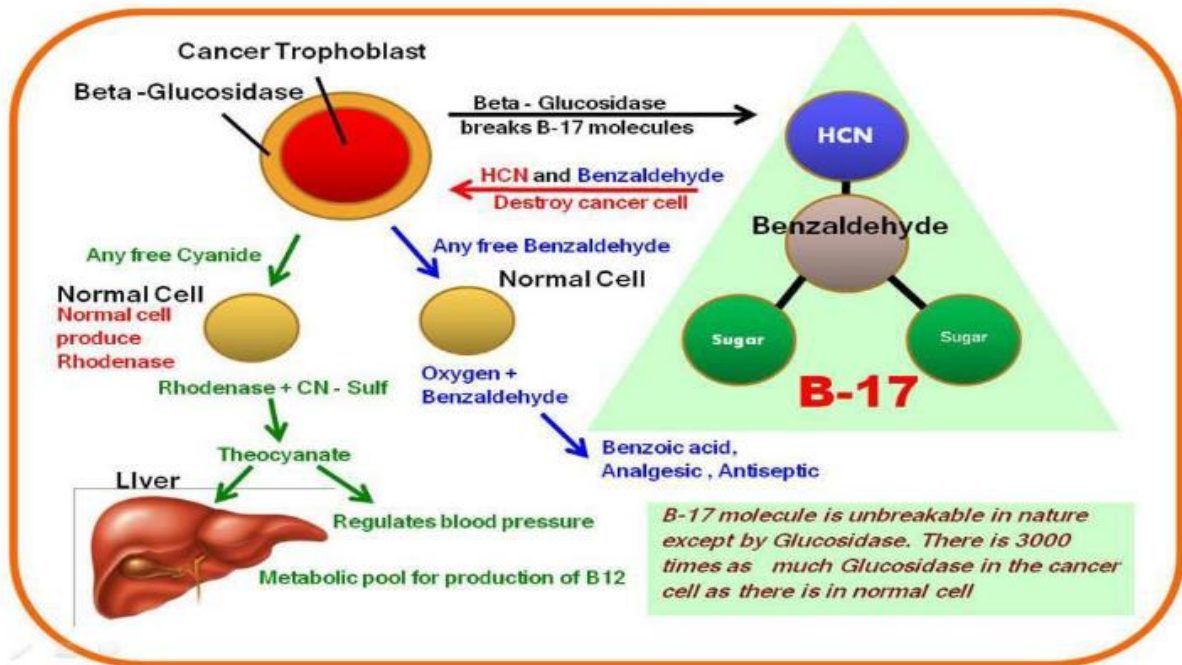


Figure 3: Mechanism of action of Amygdalin/ Laetrile.

Pharmacological effects

Anti-asthmatic effects

Amygdalin was used for prevention of asthma in ancient Korean medicine. After oral administration, laetrile is degraded into benzaldehyde and hydrocyanic acid which slows down respiratory movement and produce anti asthmatic and antitussive effect. Amygdalin kills the type 2 helper T cells which result in the case of inhibition of Th2 response to allergen.²¹

Action on human renal fibroblast

Laetrile inhibit certain expression of type 1 collagenase and human kidney fibroblast production, which encourage apoptosis of human renal fibroblast.²²

Role in immunity

Laetrile can promote polyhydroxyalkanoates induced human T lymphocytes proliferation which secrete IL-2 and interferon and prevent TGF- B1 thus enhancing immune response. Amygdalin helps in the expression of regulatory T cells in the treatment of Psoriasis, atherosclerosis, can also expand the lumen area and reduce aortic plaque.²³

Effect in digestion

Studies found that Prunasin is the major component of amygdalin in digestive fluids which was incubated in a caco-2 cell culture system. It was decomposed into the mandelonitrile by β -glucosidase and hydroxylase through

the small intestine producing hydroxymandelonitrile. Amygdalin decomposes benzaldehyde through enzyme decomposition which can inhibit pepsin activity and affect the digestive system. Also, it is reported that amygdalin has a good therapeutic effect on rats with chronic gastritis and chronic atrophic gastritis.²⁴

Analgesic effect

Studies demonstrated that amygdalin isolated from *Prunus armeniaca* can reduce formalin-induced pain in rats which may involve with inflammatory cytokines such as tumor necrosis factor-TNF and interleukin-1 (IL-1) as well as c-Fos.³

Anti-inflammatory effects

Studies indicated that Amygdalin has anti-inflammatory effects due to reduction in expression of proinflammatory cytokines pro-IL-1 beta.²⁵

Hypoglycaemic effects

Amygdalin prevents the alloxan induced hyperglycemia due to scavenging of the harmful and highly sensitive hydroxyl radical which was produced from alloxan.²⁶

Antitumour effects of amygdalin

It was first found by Schrader in bitter almond in 1803. Robiquet and Butron discovered and purified amygdalin and called it Leibig in 1835. It was first used in cancer treatment in 1845 by Russian doctor. In Mexico, it was produced in large quantities as an anticancer drug.

Amygdalin can start apoptosis in human promyelocytic leukemia (HL-60) cells. It repressed production of human colon cancer SNU-C4 cell and can start apoptosis by regulating expression of Bax and Bcl-2 in prostate cancer. Amygdalin can reduce existence of HeLa cells in rats through the endogenous mitochondrial pathway which starts the apoptosis of HeLa cells. The detection results of human genome microarray showed that 573 genes of HeLa cells had differential expression in amygdalin treated group compared to control group. JNK-c jun pathway is involved. The second line of defence has been proposed to be by vitamin B17.^{27,28}

Lung cancer

Qian et al suggested that amygdalin exerts its anticancer effects in NSCLC by inhibiting AKT- m TOR signaling pathway. Amygdalin was used to treat high metastatic cell lines H1299/M, and PA/M and found that proliferative and migration abilities were all inhibited. Amygdalin was found to downregulate integrin beta 1, beta 4, ILK, beta catenin factors expression known to promote cancer metastasis. It upregulate Cadherin E expression and reduce phosphorylation of AKT.²⁹

Bladder cancer

Makeravic et al detected vascular tumour cell adhesion and migration of collagen and tumour cells and observed amygdalin effects on integrin alpha and beta subtype, ILK (integrin-linked kinase) and FAK(Focal adhesion kinase) after treatment of bladder cancer cells with specific doses of amygdalin. They found that adhesion and migration cells were inhibited after amygdalin treatment and also the expressions of integrin alpha and beta subtypes, ILK and FAK were decreased.³⁰

Renal cell carcinoma

Juengel et al found that amygdalin reduced the number of G2M phase or S Phase cells and significantly reduced the growth and proliferation of RCC cells. It also markedly reduced cell cycle activators e.g. cyclin B, cdk 1, E-cadherin and N-cadherin.³¹

Cervical cell carcinoma

Chen et al proposed that amygdalin had pro-apoptotic effects on HeLa cervical cancer cells mediated by endogenous mitochondrial pathway.³²

Breast cancer

Studies have shown that amygdalin exerted anti-proliferative and cytotoxic effects on estrogen receptors (ER)-positive MCF7 cells, and MDA-MB-231 and Hs578T triple-negative breast cancer (TNBC) cells. It downregulated B-cell lymphoma 2 (Bcl-2), upregulated Bcl-2-associated X protein (Bax), activated caspase-3 and cleaved poly ADP-ribose polymerase (PARP).

Amygdalin exerts cytotoxic effects on human breast carcinoma cells, inhibits proliferation of MCF7, MDA-MB-231 and Hs578T cells. In some studies, MTT assay was done in which upon treatment with various amygdalin concentrations for 24 hours, amygdalin exerted cytotoxic effects on ER-positive MCF7 as well as MDA-MB-231 and Hs578T TNBC cells.³³

In some studies, cells were treated with amygdalin at various concentrations for 24 hours and the levels of Bcl-2, Bax, PARP and pro-caspase-3 were determined by immunoblot analysis. It was found that amygdalin increased the expression of pro-apoptotic protein Bax and decreased that of anti-apoptotic Bcl-2. These data demonstrate that amygdalin induced apoptosis in Hs578T cells in which signaling pathway through p38 MAPK may be involved.³⁴ Amygdalin inhibits adhesion of Hs578T breast cancer cells. The results demonstrate that amygdalin effectively inhibited the adhesive phenotype of Hs78T breast cancer cells. The level of integrin $\alpha 5$ was decreased by amygdalin treatment.³⁵ Altogether, amygdalin is proposed to have pro apoptotic and antiadhesive effects on breast cancer cells. Hence, this indicates a potential for amygdalin in future to be used as a chemotherapeutic agent for breast cancer cure especially TNBC.

Prostate cancer

Makerovic et al exposed prostate cancer cell lines to amygdalin and found cell proliferation was inhibited by marked decrease in G2M phase and S phase cells by flow cytometry.³⁶

Colon cancer

Amygdalin also affects the cell cycle of human colon cancer. Park et al.³⁷ showed significant differences in gene expression of SNU-C4 cells after amygdalin treatment. It was reported that amygdalin downregulated cell cycle genes: ATP binding cassette, exonuclease 1, topoisomerase in SNU-C4 human colon cancer cells. Studies found that amygdalin treatment proved to be valuable in cancer cure, causing inhibition of cell growth and down-regulation of telomerase activity in human cancer cell lines by increasing β -glucosidase activity.³⁸

Ovarian cancer

In some studies, Amygdalin, at the highest dose (10,000 $\mu\text{g/mL}$), stimulated the release of estradiol-17 β by ovarian GCs (granulosa cells), in comparison to the untreated control cells. But no significant changes in progesterone release by GCs were observed after addition of amygdalin.³⁹

Amygdalin toxicity

Experiments of amygdalin has proved that the toxicity of oral administration route is far more than the intravenous

since intestinal bacteria contain beta-glucosidases that activate the release of cyanide after ingestion of laetrile. But when laetrile is injected little breakdown occurs to yield the hydrogen cyanide. The mean lethal dose (LD50) of amygdalin in rats was reported to be 880 mg/kg body weight (BW) by oral administration. The LD50 of intravenous injection in mice are 25g/kg, while intraperitoneal injection are 8 g/kg.⁴⁰

A lethal dose of cyanide was considered to be between 5 to 3.5 mg/kg of body weight according to Committee on Toxicity (2006).⁴¹ Cyanide blood levels of higher than .05 mg/dl produce toxic effects, with fatalities reported at levels of 3 and higher. A level of 3.2 mg/dl was reported to be very high according to Taylor et al (2006), Bradford et al recommendations advised maximum of 15 apricot kernels to be consumed in a 150-lb adult. Suchard et al published the first case of cyanide toxicity from eating apricot kernels.⁴²⁻⁴⁴

Symptoms of Mild toxicity are Nausea, dizziness, drowsiness, headache, metallic taste. Moderate toxicity: Loss of consciousness for short period, convulsions, vomiting, cyanosis. Severe toxicity: Deep coma, dilated non-reactive pupil, deteriorating cardio-respiratory function. Acute toxicity can occur in adults who consume more than 20 apricot kernels.⁴⁵

Drug interactions: A potential life-threatening interaction can occur if amygdalin is taken together with high doses of vitamin C.⁴⁵

Sauer et al reported a case of a 4-year-old child receiving treatment for malignant brain disease whose parents gave amygdalin intravenously and orally in the form of apricot kernel.⁴⁶ This resulted in acute cyanide poisoning that finally led to a severe encephalopathy. Thereafter, the child's condition improved rapidly after sodium thiosulfate administration. Also it proposed that the cyanide toxicity leads to the dysfunction of oxidative phosphorylation within the cells. Hence, the risk benefit balance was thought to be doubtful in some studies.

According to literature, amygdalin has numerous pharmacological functions. But the role of amygdalin as anticancer agent is controversial. Some of the clinical trials urge that amygdalin has no steady anticancerous effects rather headache and gastrointestinal reactions were its adverse reactions after large doses.⁴⁵ The adverse effects from cyanide poisoning led the FDA in USA and European commission to ban the use of laetrile. However, various studies in the recent past have also proved the clinical value of amygdalin as therapeutic and antitumor agent though further research are needed to reveal the pharmacological importance of the compound in modern medicine. Condemnation of Laetrile based on result interpretation has been thought of as premature as mentioned in some studies like Ellison et al reviewed cases where Laetrile was thought to have worked.⁴⁷ Moss and Griffin concluded that Laetrile was effective in more

than 80% of the cases and a positive response was noticed in about half the cases.^{48,49} The safety of Laetrile was examined by FDA which found no significant problems but could not find evidence of its effectiveness. Thus FDA became convinced that Laetrile was worthless for cancer therapy. Many cancer patients demanded the right to use laetrile and over 20 state legislatures opposing the FDA's decision legalized laetrile for marketing and consumption. The lack of a control group in majority of studies made the conclusions highly speculative. Some researchers concluded that amygdalin has been incorrectly deemed ineffective and its positive effects have been ignored.⁵⁰ Recent research in Japan has shown that amygdalin induces apoptosis in prostate cancer cells.⁵¹ Amygdalin also has the risk to cause body poisoning, but in a short-lasting treatable way.⁵² as compared to modern cancer therapy of chemo radiation. Some isolated tribes all over the world such as the Abkhazians, the Hopi, Navajo Indians, the Hunzas, the Eskimos etc. did not have any cancer cases which turned out that they had a diet in common rich in amygdalin.⁵³ Due to its toxicity, a semi-synthetic preparation of amygdalin, called laetrile, was patented and marketed as a safer cancer treatment. So, vitamin B17 can act as "natural chemotherapy" in cancer treatment. The constituents in apricot kernels deserve to be thoroughly researched as an adjunct to cancer treatment. We have tried to compile data from PUBMED, NCBI, SCOPED, you tube links, Cochrane database etc.

CONCLUSION

Amygdalin is a widely sourced natural product that has shown antitumor activity and is comparatively low priced, it might come up as a future antitumor drug with synergistic effects. A number of studies have shown that amygdalin has a contributory role in the treatment of diabetes, cancer, immunosuppression and atherosclerosis. Randomized controlled clinical trials should establish the efficacy of laetrile along with standardization of acceptable formulations, dosage and the methods of administration. Both cell line studies and human trials should be carried out to explore other benefits of laetrile and to promote the product as nutritional supplement. The pharmacological activity of amygdalin is clear, but more systematic indepth research is needed with well - designed controlled clinical trials to be approved for human use.

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