

## Review Article

# Amygdalin-Therapeutic Effects and Toxicity

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## Abstract

Amygdalin is a cyanide glycoside existing naturally in many fruits, predominantly in bitter almond, peaches and chemically as laetrile. It has attracted many cross talks amongst researchers especially on its anti-cancer potential and its associated cyanide toxicity. Quite number of reports have demonstrated its chemotherapeutic effect on various types of cancer cells *in vitro* with very few *in vivo*. However, its long standing several clinical failures and cyanide toxicity on variable dosage made it generally unacceptable. However, amygdalin given at the right dosage orally may not lead to toxicity, but this has not been quantified yet, and it is often influenced by the activity of microbial gut content. Its pharmacological activities have been studied extensively, but its anti-tumor activity is still inconclusive. New clinical studies with emerging

scientific approaches may seek to give the satisfactory answers about its anti-tumor effects. This review discusses the metabolism, various pharmacological activities, toxicity and current understanding on the anti-tumor effect of amygdalin.

**Keywords:** Amygdalin; Cyanide toxicity; Anti-tumor; Metabolism

## 1. Introduction

Amygdalin was first isolated in 1830s from bitter almond by Robiquet and Boutron-charlard and later found to occur naturally as cyanogenic glycoside in fruits and seeds of apricots, peaches and bitter almond [1, 2]. The enzymatic hydrolysis of amygdalin yields benzaldehyde and hydrocyanic acid while its acid

hydrolysis produces a single product gentibiose. Amygdalin also exhibits pre-hepatic metabolism producing prunasin in the intestine [3]. It has been a subject of debate whether amygdalin causes tumor regression or is it toxic at the rightly administered dose rendering it a toxic chemical rather than a therapeutic drug. Many *in vitro* experiments have demonstrated that it is capable of inducing apoptotic cell death and causing cell cycle arrest or delaying its progression in several cancer cell lines [4, 5]. Few *in vivo*-experiments on the anti-tumor effects of amygdalin reported reduced growth of Hela cells xeno graft *in vivo* in nude mice [4].

However, amygdalin faced critics as a therapeutic drug from many authors because of its several, persistent clinical trial failures [6]. Laetrile, a chemically modified form of amygdalin which was reported to work earlier also failed in many clinical trials, but it was suggested that there may be difference between both [7]. Studies conducted to evaluate the toxicity of amygdalin revealed its toxicity especially when administered orally, and this led to its ban by FDA in 1979 [2]. More so, the family of anaerobic bacteria residing in the intestinal gut are capable of releasing cyanide in the intestine from the breakdown of amygdalin [2, 8]. However, rhodanese which is a ubiquitous enzyme found in the mitochondria of many organisms is capable of converting the high cyanide content resulting from amygdalin to a harmless thiocyanate [7]. Amygdalin has a wide range of pharmacological activities including analgesic and anti-asthmatic effects. This review seeks to discuss the anti-cancer effect and toxicity of amygdalin.

## 2. Metabolism of Amygdalin

The first complete enzymatic and acid hydrolysis of amygdalin was reported by Haisman and Knight in 1967. When amygdalin is subjected to  $\beta$  glucosidase it yields glucose and prunasin. The prunasin is further hydrolyzed to give glucose and another compound

called mandelonitrile. The product is non-enzymatically converted to benzaldehyde and hydrocyanic acid. The acid hydrolysis of amygdalin yields a single product gentibiose (a disaccharide with  $\beta$  1-6 linkage). Michaelis-Menten kinetics can be employed to determine the stages of enzymatic action involved. Three enzymes which catalyzed at three different stages have been identified and they include: amylase lyase, prunasin lyase and hydroxyl lyase. In addition, the enzymes can be further purified on a thin layer chromatography [1, 9]. Hydrocyanic acid and glucosidase are the two major key participants necessary for amygdalin to induce apoptosis and inhibit proliferation of cancer cells [7]. Furthermore, the glucosidase performance is highly improved in the presence of lactate released during the anaerobic respiration by cancer cells [2]. HCN is also capable of destroying the cancer cells by increasing the acidic content of the cell and making lysosome to release its enzymatic content, thereby leading to lysis of the cells [7]. Amygdalin was found immediately in the blood stream of rats after 5 min. of administration [10]. Pharmacokinetic study of amygdalin suggested that amygdalin may undergo two different metabolic pathways [3]. The first is the pre-hepatic or first pass metabolism of amygdalin to prunasin in the proximal part of the intestinal gut and the second pathway involves the direct metabolism to cyanide and benzaldehyde by the bacterial gut which constitute the major toxicity from cyanide.

The metabolism of orally administered amygdalin under a simulated gastro-intestinal cell culture revealed that it was degraded first to prunasin and later to mandelonitrile by  $\beta$  glucosidase after which it was hydroxylated to hydroxymandelonitrile in the small intestine [11]. No cyanide or benzaldehyde was produced in this phase, and this indicates that cyanide is likely formed at the lower intestine which is rich in

microflora [11]. The plasma concentration of amygdalin can be determined by Liquid Chromatography-Mass spectrometry (LC-MS) method [10].

### 3. Pharmacological Activity of Amygdalin

#### 3.1 Anti-asthmatic effects

Amygdalin serves to relieve asthma due to its decomposition which produces hydrocyanic acid that could relax the respiratory movements by inhibiting the respiratory center to a certain extent. It was also seen to enhance the synthesis of pulmonary surfactant in animal experimental model suffering from respiratory disease syndrome [12, 13]. Amygdalin was reported to give protection to type II alveolar epithelial cells (AECIIs) isolated from premature rat lungs which were placed under hyperoxia condition. This condition inhibited the proliferation of AECII and reduced the mRNA levels of surfactant pulmonary in the AEC II in vitro, thus inducing lung injury in the premature rats. Amygdalin at a concentration of 200 micromol/L worked best by stimulating the proliferation of the premature rat AECII and elevating the SP mRNA levels [14]. In addition, Semen Armeniacae Amarum (SAA) containing amygdalin as active ingredients also has anti-asthmatic effect on mouse model of allergic asthma through OVA induction [12]. The SAA was said to lower the interleukin (IL)-4 and suppress the type 2- helper T cell (Th2) activity. Airway hyperreactivity (AHR) and airway inflammation manifesting from the asthmatic effects were reduced, which may be due to the alteration of Th2 response against the allergen.

#### 3.2 Analgesic effect

The analgesic and anti-inflammatory activities of amygdalin were previously tested with in vitro lipopolysaccharide (LPS)-induced cell line and a rat model with carrageenan-induced ankle arthritis [15]. The amygdalin which was extracted from the seeds of rosaceous stone fruits inhibited the expression level of

prominent molecular markers of pain and inflammation including necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) and diminished the hyperalgesia of the arthritic ankle at a concentration of 0.0005 mg/kg. It was also demonstrated that amygdalin extracted from *Prunus armeniaca* can relieve formalin induced pain in rats when the dosage level is less than 1 mg/kg which may be also be through influencing the expression of inflammatory cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) [13]. Furthermore, it also reduced the expression of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS) which consequently decreased prostaglandins E2 and nitric oxide levels, thus bringing about anti-inflammation and analgesic effect [16]. The same effect was also reported with hot plate and acetic induced writhing test where amygdalin injected mice did not show any jumping response or morphine-characteristic tail-erecting response [17].

#### 3.3 Enhancing the immune system of an organism

Amygdalin has an anti-atherosclerotic effect by suppressing the anti-inflammatory response through stimulating the immunomodulatory effect of regulatory-T cells (Tregs) which consequently lead to loss of atherosclerotic plaque and also enlarging the lumen area [18]. It was also reported that it promotes peripheral blood lymphocytes stimulated by polyhydroxyalkanoate PHA, secretes IL-2 and IFN- $\gamma$ , thereby assisting with the immune function [13]. Peptide T (PT) an octapeptide which is often referred to as an analogue of amygdalin due to similar peptidomimetics has been demonstrated to be effective in treating psoriasis [19]. The PT was demonstrated to stimulate the over expression of TGF- $\beta$ , HSP70 and  $\alpha$ -v integrin, and reduction of ICAM-1 in human keratinocyte cells [19]. In addition, three analogues derived from amygdalin having the peptidomimetics and lacking the cyanide group have been shown to have the same biological

behaviors as PT [19]. They have the same immunomodulatory effects on human keratinocyte cells which suggest their uses in treating psoriasis.

### 3.4 Amygdalin effects on the digestive system

The breaking down of amygdalin in the human digestive fluids and its metabolite absorption in the small intestine under stimulated GIT digestion model and human intestinal culture have shown the impact of amygdalin on the intestinal wall and the risk associated with its intake from food [11]. Benzaldehyde derived from amygdalin can inhibit pepsin activity and consequently affect the digestive function [13]. It was demonstrated that the administration of pepsin to a CCl<sub>4</sub> treated rat at a dose of 500 mg/kg inhibited the level of AST, ALT, and increased the time for euglobulinolysis. In addition, the connective tissues of rat liver proliferates less in the presence of pepsin hydrolysate of almond water, but the proliferation was un affected after inducing the rats with D-galactosamine due to restored level of AST and ALT [13]. Amygdalin was also reported to show therapeutic effects on chronic gastritis and chronic atrophic gastritis induced rat [11, 13].

### 3.5 Anti-angiogenic effect

Amygdalin was reported to inhibit angiogenesis in the endothelial cells of streptozotocin-induced diabetic rats by reducing the number of matured microtubules in the aortic ring of the amygdalin treated diabetic rats [20]. The aortic ring of the rat without amygdalin treatment migrated and proliferated after 7 days of incubation as revealed through optic microscopy. It was also suggested that the anti-angiogenic effect of amygdalin may also play a role in its tumor suppression activity [20].

## 4. Cyanide toxicity from Amygdalin

The benzaldehyde which is responsible for the aroma and flavoring in fruit can be hydrolyzed to benzoic acid and hydrocyanic acid (HCN). The latter one is mainly

responsible for toxicity when amygdalin is ingested orally or through some other routes. The process involves inhibiting cytochrome oxidase which in turn affects the electron transport chain and mitochondria [2]. Taking amygdalin in its natural form, which is cyanogenic glycoside, could easily result into toxicity because of the action of beta glucosidase in human body [2]. It was stated that 4 g of amygdalin per day after oral administration in human is enough to cause systemic toxicity [13]. Cyanide also has the ability to reduce the ATPs level of the brain and increase the lactate formation by impairing the Kreb's cycle [21]. Several cases of amygdalin toxicity have been reported either through consumption from its source fruits or the synthetic compound laetrile. Only two out of ten mice survived when they were injected with 500 mg/kg of amygdalin intravenously [13]. The toxicity experience in mice could be as a result of breaking down of amygdalin to cyanide by the  $\beta$  glucosidase activity of the intestinal microbes in the mice [22]. A study was conducted by NCI where six cases of its toxicity were stated, and this led to the ultimate ban of amygdalin in 1979 by the FDA [2].

However, several studies have shown that amygdalin administered through other means except the oral method may not lead to toxicity. One of the earlier studies conducted revealed that cyanide toxicity was seen in both the conventional and germ-free rat when amygdalin was given orally, but no toxicity was experienced when administered parentally [23]. It was recently reported that a 4-year-old boy was given amygdalin without a specific dosage through IV and orally from apricot kernels, and the serum cyanide level increased drastically leading to cyanide poisoning [1]. The major symptoms of cyanide poisoning at earlier stage include mild irritation, anxiety, drowsiness and dizziness. Convulsion, hypotension and cardiovascular edema may be experienced at the later stage of cyanide

poisoning [21]. More so, it was reported that high dose of amygdalin may not express high toxicity in the body [1]. A case of a patient who took two times his normal dosage orally but did not show any sign of cyanide toxicity was stated. Cyanide toxicity may vary from one person to another and may be influenced by age, obesity, dosage, nutritional status and routes of administration [2]. Many of these factors affect the population of microbial enzyme responsible for amygdalin degradation. IV route leads to less cyanide toxicity because of rhodanese activity and absence of  $\beta$  glucosidase activity [24]. Rhodanese (thiosulfate sulfur transferase) is capable of converting cyanide released from amygdalin to a harmless thiocyanate using thiosulfate and its distribution in the tissue is influenced by the level of exposure of cyanide to the body [7]. Many studies suggest that rhodanese is much presence in the normal tissue but absent in the cancer cells [4].

Increase in body weight decreases the number of bacterioidetes, but high fiber contents diet increases the microbe population in the gut [24]. Vitamin C has been reported to speed up the conversion of amygdalin to cyanide *in vitro* and reduce the storage level of cysteine needed for detoxification process [25]. The intake of Vitamin B<sub>12</sub> and sulphur containing amino acid like methionine and cysteine may also influence cyanide detoxification because they affect the activity of the rhodanese enzyme [26]. Vitamin B<sub>12</sub> acts as chelators, binds to cyanocobalamin and aids cyanide excretion through the kidney. It is used as cyanide antidote because it helps to activate the rhodanese detoxifying process [26]. A study conducted revealed that hydroxocobalamin can effectively reduce the cyanide toxicity resulting from amygdalin. The rats administered with hydroxocobalamin after given amygdalin on a therapeutic dose of 20 mg/kg body weight showed a significant reduction in the serum lactate and cyanide concentration in relative to the control [27]. In addition,

the histological examination of the liver revealed no morphological changes compared to the rat without antidote. The hydroxocobalamin was also reported to reverse the high packed cell volume (PCV) and reduced blood pH seen in the rats after amygdalin administration. Some rats fed with amygdalin without following with hydroxocobalamin did not survive through the experimental period due to cyanide poisoning while no death was recorded with those fed with antidotes. Many specific antidotes including nitrite, methemoglobin and cobalt compounds serve as cyanide antagonist, and they have been used in treating cyanide poisoning [28]. However, supportive treatment is mostly employed especially when the signs and symptoms cannot be traced to a history [28]. Generally, the same method for treating cyanide in-toxication from other sources like cassava and cyanide compounds can also be extended to that from amygdalin consumption.

## 5. Effect of gut microbial flora on Amygdalin

The metabolism of a drug or any foreign compound entering the body is impacted by the GIT, lumen, gut and gut microbes especially when ingested orally [2]. Firmicutes, Bacterioidetes and Actinobacteria are the main groups of bacteria contributing to the release of cyanide in the intestine, and they are mainly anaerobes [2]. The gut constitutes many enzymes including nucleases, lipases, transferases, and peptidases and enzymes of microflora [2]. The intestinal  $\beta$  glucosidase and microbial  $\beta$  glucosidase have been demonstrated to work on different substrate and give different products. The  $\beta$  glucosidase which are lactasephlorizin hydrolase (LPH) and cytosolic  $\beta$  glucosidase (CBG) found in the intestinal mucosa cleave glycosidic linkages and act on other compounds like bile and fatty acids to yield carcinogens. The intestinal  $\beta$  glucosidase can also convert amygdalin to prunasin and no hydrocyanic acid is formed [1].

The other  $\beta$  glucosidase from the microbes residing in the gut majorly hydrolyze amygdalin to HCN. Several studies have demonstrated that the enteric bacteria can hydrolyze amygdalin into cyanide and this is proportional to the amount of microbial gut content [8]. In addition, toxicity due to amygdalin hydrolysis was greatly reduced when the intestinal microbial growth was inhibited in mice administered with 300 mg/kg while that of untreated mice caused toxicity and showed a death rate of 60% higher [29, 30]. Human stool was shown to hydrolyze about 50% of amygdalin to cyanide because of the excess flora present compared to that of mouse and monkey [8]. Bacteroidetes are mostly employed to produce glucosidase. Prebiotics and probiotics influence and regulate the bacterial population in the gut [31]. Prebiotics are biological molecules while probiotics are organisms that modulate the activities of gut microbiota for the benefit of the host. prebiotics are capable of binding or absorbing carcinogens and reducing risk of cyanide toxicity from amygdalin. Lactobacillus and Bifidobacterium have been shown to reduce the  $\beta$  glucosidase activity from Bacteroidetes [31].

## 6. Anti - Cancer Activity of Amygdalin

Amygdalin is believed to be abundant in the seeds of some plants including apricots, apples, almonds and peaches and this gives an opportunity to be tested on many cancer cells. Chen et al., reported for the first time with cervical cancer that amygdalin has an apoptotic effect on cervical cancer Hela cells line. It was reported that amygdalin treated Hela cell lines was first stained with 4,6 Diamino-2 phenyl indole (DAPI) after which it was treated with annexin V-FITC and propidium iodide, respectively. The actions of anti-apoptotic BcL-2 proteins were reduced and that of pro-apoptotic Bax proteins were increased. There was also an increase in caspase activity and the initiation of intrinsic apoptotic pathways. It was suggested that amygdalin has a

therapeutic effect on cervical cancer through reducing viability of the Hela cells *in vitro*. In addition, same result was also reported for a Hela cells xeno graft *in vivo*. More so, the effect of amygdalin extracted from *Armenlacaee semen* belonging to prunasin family was also previously reported to have been tested on DU 145 and LN CAT prostate cancer cells [32]. An increase in caspase 3 enzymes with the down regulation of anti-apoptotic BcL-2 protein and up regulation of Bax proteins were stated. It is believed that the amygdalin extract caused an apoptotic cell death human prostate cancer cell [32].

The chemo-preventive potential of amygdalin was also tested on breast cancer cell *in vitro*. It was reported that it caused the cytotoxicity of estrogen receptor (ER)-positive MCF7 cell, MDA-MB-237 and Hs 578T triple negative breast cancer cells (TNBC). Also, the same actions were noticed with BcL-2, Bax, and caspases [33]. In addition, p38 mitogen activated protein kinases (p38 MAPK), a pro apoptotic signaling molecule was stimulated and further amygdalin treatment also inhibited the adhesion of Hs 578T TNBC. It was shown that amygdalin may be effective towards breast cancer cells. Similar case of adhesion was also reported in bladder cancer cells [5]. A distinct reduction in adhesiveness of tumor cells UMUC-3, RT112 cells and TCCSUP cells were reported upon 24 hours or 2 weeks' treatment with amygdalin. A reduction in migration was noted for the first two cancer cells but TCCSUP showed an increase in migratory property [5]. The authors suggested that anti-cancer activity of amygdalin may be specific to some cancer cell lines. The same case was reported with cervical cancer cells where amygdalin showed a therapeutic effect against the Hela cells line but not with the FL cells [4].

Racemization of amygdalin to neo-amygdalin in aqueous solution was reported to hinder its anticancer



activity in a promyelocytic Leukemia cell [34]. It was duly reported that HPLC chromatography revealed the amygdalin extract from *Persicae semen* as active D form and so, the extract was boiled to inhibit the epimerization process before applying it to a promyelocytic Leukemia (HL-60) cells. Increase in the death of the cells were also recorded which was suggested to be from apoptotic process. In addition, morphology changes in the nucleus and DNA fragmentations of the cells were also said to have been noticed [34]. Therapeutic effect of amygdalin was also demonstrated for Non-Small Cell Lung Cancer (NSCLC) cells line H1299 and PALM in vitro [35]. Anti-proliferation of the cells occurred at high concentration of amygdalin, inhibition of migration and invasiveness occurred at the low concentration of the solution.

### **6.1 Amygdalin delays cell cycle progression in some cancer cells**

Amygdalin also exhibits its anti-tumor activity through influencing or modifying some proteins involved in the cell cycle. Besides inducing apoptosis of PC3 and LNCaP cells in prostate cancer after treatment for both 24 hrs and 2 weeks, amygdalin was also reported to have caused reduction in G2/M phase cells and elevation of G0/G1 phase cells [5]. In addition, the modulation of some cell cycle proteins like cyclins, cdks were also stated. The same case was reported in colon cancer cells where there was down regulation of some cycle proteins mainly the exonuclease, topoisomerase and binding protein in amygdalin treated SNu-C4 cells [36]. The authors employed cDNA microarray analysis to express the downregulation of the proteins and a decrease in the level of their mRNAs was also reported using RT-PCR analysis.

## **7. Amygdalin On clinical trial**

One of the earlier advocators of laetrile (chemical modified form of amygdalin) reportedly says “laetrile  
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works”, this was one of the three reasons he gave for its survival over many years [37]. More so, Sir Ernst Krebs jr who was said to have considered cancer has a vitamin deficiency proposed that amygdalin might be the missing vitamin. He made it public that laetrile is vitamin B17 and this was accepted by many Americans and political figures in the mid-1970s was later refuted critically after a while.

A recently published review “Amygdalin: quackery or cure” by Blaheta et al., provided a general and current knowledge on amygdalin trials. It was reported in the review after considering junks of journals from Pubmed data base and relevant internet sources that there is no appropriate and convincing evidence that amygdalin may put end to this deadly, systemic disease and thus, this resolution remains inconclusive. It was said that the clinical trial in cancer patients revealed that it did not induce any apoptosis or cause tumor regression in cancer cells especially at the last stage. However, the authors also concluded that a purified amygdalin upon administration does not cause toxicity to normal cells. Furthermore, the author did not ascertain the therapeutic potential of amygdalin upon multiple administration.

Another group of researchers from Cancer Networks disclaimed laetrile, a chemical modified form of amygdalin as a cure to cancer. It was attributed to the same false believes people have about AIDS as disease promulgated to eradicate the black people, and that of autism to have been caused from vaccines. Laetrile was reported to have failed in 175 clinical patients and in 20 years’ animal studies [6]. However, its recent widespread usage was attributed to fraudulent internet sources resurfacing it as the main cure of cancer rather than alternative therapy [6]. It was also stated that laetrile could not be supported with any clinical data after examining about thirty reports from different publications [7]. The author argued that there might be a

difference between amygdalin and its presumed chemically derived compounds laetrile sold in the market.

**8. Discussion and Future perspective**

Amygdalin’s role has as cancer cure has created critical debate amongst scientist with many contradictory publications and cross talks on its toxicity. Several experimental results especially *in vitro* supported the anti-tumor activity of amygdalin. Nevertheless, its anti-tumor activity is inconclusive due to its clinical trial failures and toxicity on large dosage [13, 38, 39]. Amygdalin was well known among the cancer patients in the 1970s where it was mainly used as one of the complementary and alternative medicine to cancer [1, 6]. However, its usage died down after a few decades but got reawakened recently due to internet promotion which many researchers believed is a fraud because of

substandard scientific reports regarding its efficacy [1]. Many critics on amygdalin still relied on aged scientific evidences which might have restricted its research scope [1]. The anti-cancer potential of amygdalin should not be underestimated especially when its apoptotic action has been demonstrated on various cancer types *in vitro*. In addition, its therapeutic effect on Hela cells xenograft *in vivo* has also been carried out [4]. It is established that no recent thorough clinical studies have been carried out on its anti-tumor effect and toxicity, and many new scientific approaches have not been targeted toward its studies [1, 13]. Antibody may be useful in safe delivery of amygdalin without toxicity, but no clinical study has proven that to enable its therapeutic use [2]. Up to this point, there is no satisfactory answer on its anti-tumor effect and toxicity, but we hope to clear this indecisiveness after enough *in vivo* and clinical studies.

| Amygdalin effects   | Cancer cells  |
|---|---|
| Down regulation of Bcl-2 protein and up regulation of Bax proteins, An increase in caspase 3 enzymes  | Human prostate cancer cells, cervical cancer Hela cells line, triple negative breast cancer cells (TNBC),         |
| Reduction in G2/M phase cells and elevation of G0/G1 phase cells, down regulation of some cycle proteins like exonuclease, topoisomerase and binding proteins | Human prostate cancer cells and colon cancer cells  |
| Regulation of cell signaling pathways and Inhibition of adhesiveness in tumor cells   | Triple negative breast cancer cells (TNBC), bladder cancer cells and for Non-Small Cell Lung Cancer (NSCLC) cells |
| Cytotoxicity, morphological changes in cancer cells and reduction in migration of cancer cells  | Promyelocytic Leukemia, Triple negative breast cancer cells (TNBC) and Non-Small Cell Lung Cancer (NSCLC) cells   |

**Table 1:** Summary of the anti-cancer effects of amygdalin *in vitro*.

**Conflict of Interest**

The authors declare that there is no conflict of interest.

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