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Review Article:

The Pharmacological and Toxicological Effects of Amygdalin: A Review Study

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ABSTRACT

Background: Amygdalin has many pharmacological activities, such as analgesic and anti-asthmatic effects. Although several studies supported the cytotoxic effects of amygdalin on different cancer cell lines, no general agreement has been reached on the anticancer aspect of amygdalin.

Objectives: This review aims to focus on the pharmacological and toxicological effects of amygdalin and provide a reference and perspective for further investigation.

Methods: Electronic databases, including the Web of Science, PubMed, Google Scholar, and ScienceDirect, were searched to identify eligible studies on the pharmacological and toxicological effects of amygdalin and provide a reference and perspective for further investigation. Totally, 90 papers about in vitro or in vivo studies on amygdalin have been reviewed.

Results: Pharmacological activities of amygdalin have been well documented over the years; however, in some cases, dose-dependent toxicity has been reported in the human body. Since the acute toxicity of oral administration of amygdalin is far greater than the intravenous route, several in vitro and in vivo studies are needed to assess the amygdalin's pharmacological value for the induction of apoptosis and anticancer effects.

Conclusion: Amygdalin generally has dose-dependent effects. It has positive or desirable effects at lower doses and undesirable impact at a higher intake level. However, there are substantial inter-individual variations.

Introduction

Amygdalin is found in many plants, most notably in the seeds (kernels) of apricots, bitter almonds, apples, peaches, and plums (Figure 1). Amygdalin is classified as a cyanogenic glycoside because each amygdalin molecule has a nitrile group, which can be released as the toxic cyanide anion via the action of a beta-glucosidase [1]. Oral administration of amygdalin releases cyanide into the bloodstream and causes toxicity in human bodies [2]. The medicinal properties of amygdalin have been known to humans for many years. The curative properties include relieving pain, cough,

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and shortness of breath. Also, it has chronic anti-inflammatory, nerve-relaxing, and anti-atherosclerosis effects [3-7]. Various studies have shown that the correct dose of amygdalin can reduce the pain and complications of cancer cell therapy [8-13]. The toxicity of this compound is due to the formation of hydrogen cyanide (an antitumor compound) decomposed by some enzymes through oral administration (Figure 2).

In one in vitro study, the mean Lethal Dose (LD_{50}) of amygdalin in rats was found around 880 mg/kg of body weight through oral administration [14]. Several studies support the beneficial effects of amygdalin on reducing pain and other clinical complications, especially caused during cancer cells treatment [15-21]. However, due to the poor study results and the possibility of adverse effects on body organs, it is impossible to discuss with certainty the benefits of the clinical treatment with this compound.

In this review, electronic databases of the Web of Science, PubMed, Google Scholar, and ScienceDirect were searched to identify eligible studies about the pharmacological and toxicological effects of amygdalin and provide a reference and perspective for further investigation. In total, 90 papers about in vitro or in vivo studies on amygdalin were reviewed. Further research is needed to elucidate the pharmacological mechanisms of amygdalin in terms of the optimal dosage, the effective combination with other drugs, and even artificial synthesis of the active components in amygdalin for the sake of enhancing its antitumor activities and reducing its adverse effects.

Pharmacological activity of amygdalin

The pharmacological effects of amygdalin are shown in Figure 3. In recent years, researchers have emphasized the anticancer properties of amygdalin and conducted extensive studies to investigate its pharmacological effects. These studies have led to the determination of amygdalin properties and mechanisms of action.

The antitumor mechanisms

Since the 1970s, amygdalin was prescribed as a complementary drug, along with other therapies for improving the efficiency of cancer cells therapies. The antitumor effects of amygdalin mainly depend on the cell cycle process, the induction of apoptosis, the production of toxins to reduce or eliminate the activity of cancer cells, and regulating the immune function (Table 1). Recent studies have shown that choosing an effective dose of amygdalin has lethal effects on cancer cells with minimal side effects on surrounding cells [22-27].

The effect of amygdalin on cell cycle

Cell-division protein kinases are good examples for explaining cancer treatment by multi-target inhibitors. Numerous studies have been performed on the toxic effects of amygdalin on cancer cells. However, the researchers still know little about the mechanism of the cancer cell cycle, especially in the case of breast cancer. Despite many problems, efforts have continued to understand better the possible anticancer mechanism of amygdalin in the in vitro condition. In the case of breast cancer, the most effective strategies for the treatment of Human Epidermal Receptor 2 (HER2) overexpressing tumors are either blocking HER2 tyrosine kinase receptors activity or inhibiting their heterodimerization, which commonly has an aggressive phenotype and poor therapeutic outcomes [28-34].

Moradipoodeh et al. studied the effect of amygdalin on cell death and the level of pro-apoptotic Bax protein that is encoded by the *BAX* gene. They also examined anti-apoptotic Bcl-2 protein in the SK-BR-3 human breast cancer cell line. Their results showed that amygdalin might be a valuable candidate for treating breast cancer cells, especially in HER2 positive types [35]. HER2 is a protein that in humans is encoded by the *ERBB2* gene. In another study, Abboud et al. investigated the antitumor effect of amygdalin on human breast cancer cells by selective sensitization to oxidative stress. They concluded that treating MCF-7 and T47D human breast cancer cell lines with amygdalin could reduce the growth of both cells, dose- and time-dependently [36]. The effects of amygdalin on other cancer cells are described in the following studies.

According to in vitro studies, as a potent inhibitor, amygdalin could slow the growth of cancerous tumors, including prostate cancer cells, colon cancer cells, leukemia cells, lung cancer, and bladder cancer cells. In the last two cases, amygdalin has also been shown to inhibit the adhesion of cancer cells by decreased expression of integrins, reduction of catenin levels, and inhibition of the Akt-mTOR (The mammalian target of rapamycin) pathway, which may lead to the inhibition of cancer cells metastases. It has also been revealed that amygdalin in renal cancer cells increased expression of p19 protein resulting in inhibition of cell transfer from G1 phase to S phase, thus inhibiting cell proliferation [37-40]. The G1 phase is an intermediate phase between the end of cell division in mitosis and the beginning of DNA replication during the S phase. S phase (Synthesis phase) is the cell cycle phase in which DNA is replicated, occurring between the G1 phase and G2 phase. These studies showed that amygdalin could prevent tumors from malignancy by regulating cycles related to genes or cellular proteins, especially in the case of colorectal and prostate cancers.

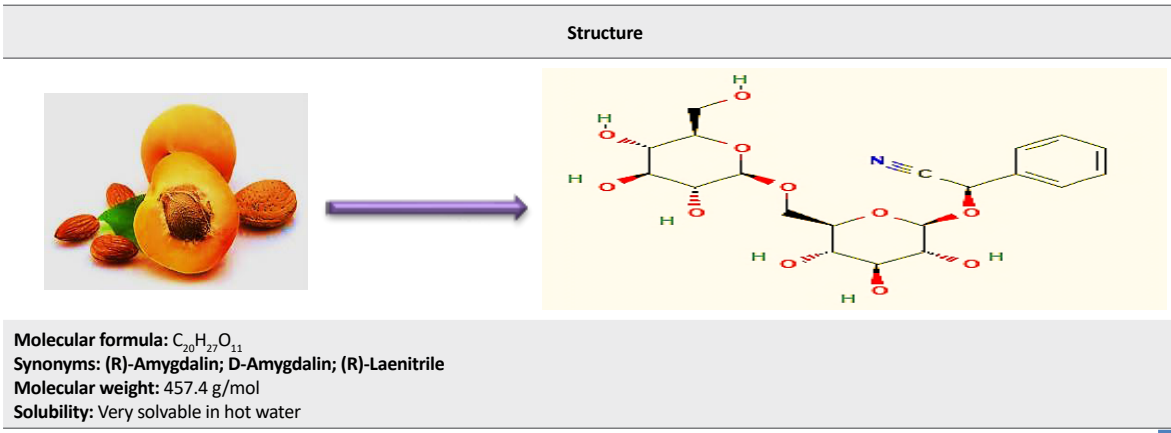

Figure 1. Chemical properties of amygdalin

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The effect of amygdalin on cell apoptosis

Apoptosis or programmed cell death is an important mechanism in treating cancer patients. Amygdalin can regulate apoptotic proteins and signaling molecules. During breast cancer treatments, amygdalin increases the planned death of SKBR3 as a human cancer cell line. Amygdalin also increases the expression of pro-apoptotic BAX protein. It decreases the expression of BCL2 anti-apoptotic protein in SKBR3 breast cancer cells. In addition, amygdalin binds to BCL2 and HER2 proteins (receptors on breast cells) through hydrogen and hydrophobic bonds with amino acids. BCL2 is encoded in humans by the *BCL2* gene. It is the founding member of the Bcl-2 family of regulator proteins that regulate cell death (apoptosis). Amygdalin may be a valuable candidate for treating breast cancer, especially in those with high levels of HER2 receptor expression [36-38]. According to these research studies, the antitumor property of amygdalin is more effective in prostate and cervical cancers [9, 22, 23, 55]. These studies show that amygdalin in relatively low dosage can reduce the growth of cancer cells or inhibit proteins that regulate the cell cycle and expression of related genes. The underlying mechanism deserves further study.

Improving the immune system efficiency

In short, amygdalin significantly increases the secretion of polyhydroxyalkanoates due to the proliferation of blood T lymphocytes. This process results in the inhabitation of secreting both Interleukin (IL)-2 and Interferon (IFN)-γ. However, Transforming Growth Factor-beta 1 (TGF)-β1 secretion is inhibited, ultimately improving immune functions. However, the regulatory role of amygdalin in monitoring the expression of T lymphocyte

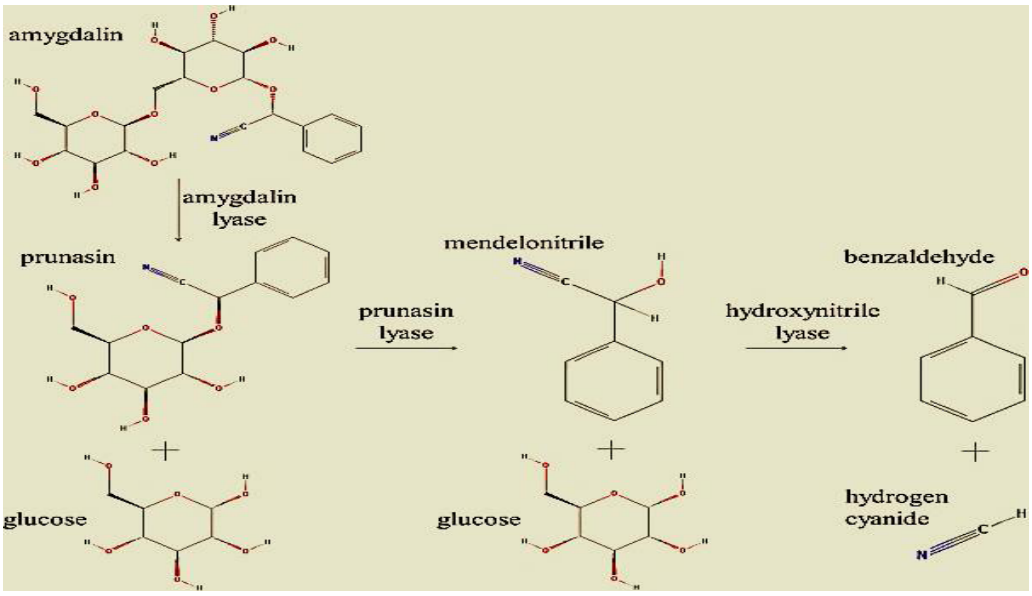

Figure 2. The reaction of amygdalin and the release of cyanide [5]

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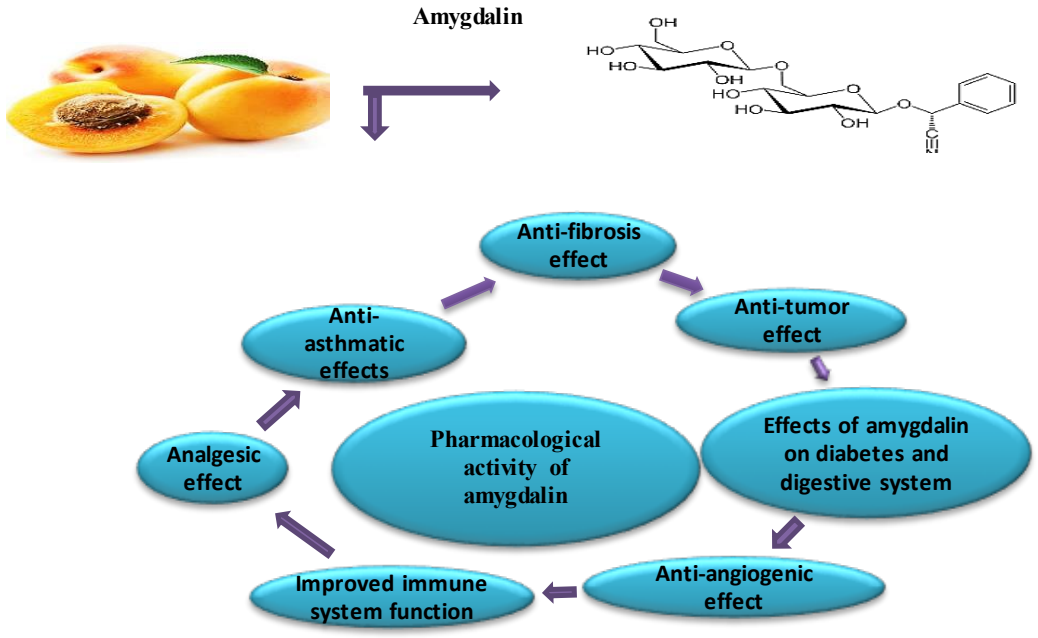

Figure 3. Pharmacological activities of amygdalin

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cells should not be overlooked. In clinical trials, 10 mg/kg of amygdalin inhibits immune cell proliferation. In other studies, this amount also reduced immunosuppressive activity in a test performed on mice that received a transplanted kidney [51-53]. Two aspects of immune system function are observed in patients after ingestion or injection of amygdalin. In some findings, amygdalin increases the efficiency of immune cells. However, in some cases, it increases the success of organ transplantation in patients [8, 41-43]. These two conflicting results require more clinical trials in animal models.

Anti-fibrosis effect

Numerous studies have documented the anti-fibrosis effects of amygdalin. Its inhibitory efficiency has been reported in renal interstitial fibrosis, hepatic stellate cell fibrosis, pulmonary fibrosis, and pancreatic fibrosis [44-47].

Table 1. Amygdalin anti-tumor mechanisms

Types	Cell Type; Dosage of Amygdalin	Treatment Time	Cellular Effects	Ref.
Lung cancer	Rats/ 5 mg/kg	28 days	Amygdalin may reduce the bleomycin-induced increase of differentially expressed protein peak intensities in rat serum.	[28]
Bladder cancer	Human cells; 10 mg/mL (UMUC-3, TCCSUP or RT112 bladder cancer cells)	24 hours or 2 weeks	Proliferation, adhesion, invasion, migration, cell cycle, cytotoxicity	[25]
Renal cell carcinoma	The RCC cell lines, Caki-1, KTC-26, and A49; 10 mg/mL	24 hours or 2 weeks	Proliferation, apoptosis, adhesion, cell cycle	[26]
Prostate cancer	LNCaP (castration-sensitive), DU-145, and PC3 cells (castration-resistant); 0.1 mg/mL, 1 mg/mL, and 10 mg/mL	24 h or 2 weeks	Proliferation, apoptosis, cell cycle Amygdalin dose-dependently diminished tumor cell growth with maximum effects at 10 mg/mL	[22]
Cervical cancer	Human cervical cancer cell line HeLa cells; 1.25 mg/mL, 2.5 mg/mL, 5 mg/mL, 10 mg/mL, and 20 mg/mL	24 hours	Proliferation, apoptosis In vivo, amygdalin administration inhibited the growth of HeLa cell xenografts through a mechanism of apoptosis.	[23]
Colon cancer	Rat model of colon cancer; 5 mg/mL	24 hours	Proliferation, cell cycle, cytotoxicity Proliferation, apoptosis	[11]
Promyelocytic Leukemia	C57BL/6 mice and AKR mice with BW5147 lymphatic leukemia; 5000 mg/kg	48 hours	Amygdalin induced apoptosis of Hs578T TNBC cells. Amygdalin downregulated B-cell lymphoma 2 (Bcl-2), upregulated Bcl-2-associated X protein (Bax),	[29]
Breast Cancer	Human breast cancer cells, estrogen receptors (ER)-positive MCF7 cells, and MDA-MB-231 and Hs578T triple-negative breast cancer cells, 4, 8, 16, 32, and 65 mmol/L	24, 48, and 72 h	activated of caspase-3 and cleaved poly ADP-ribose polymerase.	[30]

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Table 2. References for the anti-fibrosis effects of amygdalin

No.	Model and Agent	Dosage (concentration)	Activity	Ref.
1	HSC-T6 cell proliferation and fibrosis	200 µg/mL; culture; 48 h and 72 h	TGF-β↓ CTGF↓	[48]
2	HTC-T6 cells	3-10 mol/L during 48 h	PDGF↓ IGF↓	[48]
3	Anti-pancreatic fibrosis	3–60 mg/kg	Had a protective effect on rats with renal fibrosis and hypoxic brain injury	[8]
4	Anti-pulmonary fibrosis	15 mg/kg	Resulted in decreasing in collagen expression (I and III) in mice with bleomycin-induced pulmonary fibrosis	[49]
5	Anti-renal interstitial fibrosis	25-200 µg/mL; 0.055–0.437 mmol/L	Inhibit the proliferation of fibroblasts in a concentration-dependent manner in human	[50, 51]
6	Anti-liver fibrosis	200 µg/mL; 0.437 mmol/L	Hepatic stellate cells decreased the mRNA and protein expression levels of CTGF and TGF-β*	[48]
7	Anti-liver fibrosis	10−5 mol/L	significantly inhibited the expressions of platelet-derived growth factor (PDGF), insulin-like growth factor mRNA and PDGF*	[54]

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TGF-β: Transforming Growth Factor-beta; CTGF: Connective Tissue Growth Factor; PDGF: Platelet-Derived Growth Factor; IGF: Insulin-like Growth Factor.

Table 2 presents some of the references on the anti-fibrosis effects of amygdalin.

These studies emphasize that amygdalin may be used as a novel therapeutic agent for liver fibrosis.

Pain relief effect

Animal experiments have shown that amygdalin plays an important role in relieving pain and inflammation. Its mechanism of action is inhibition of prostaglandins and synthesis of nitrite oxide in reducing pain and anti-inflammatory (Figure 4) [16]. In an in vivo study, Hwang et al. showed the analgesic and anti-inflammatory effects of amygdalin on the carrageenan-induced arthritis rat model [16].

In another study, Song and Xu showed that a dose of less than 1 mg/kg amygdalin could alleviate the formalin-induced pain in laboratory mice by acting on the ex-

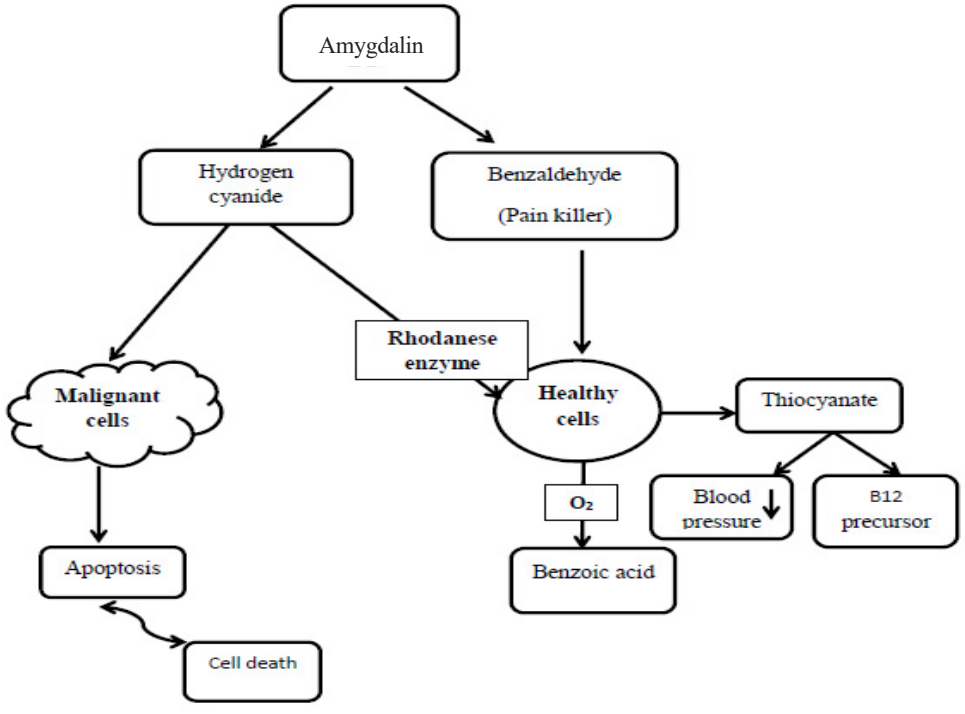

Figure 4. Possible pain relief mechanisms of amygdalin on cancer cells [16]

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pression of inflammatory cytokines like Tumor Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β) [14]. In another study, Zhu et al. observed the analgesic effect of amygdalin in mice in hot plate and acetic acid-induced writhing tests. Unlike morphine, amygdalin failed to respond properly in pain control. But, the mice treated with amygdalin did not show any jumping reaction. The analgesic and emollient effects of amygdalin were observed in these mice [55]. Data from these studies suggest that amygdalin can be used as pain relief with anti-inflammatory activity.

Improved respiratory conditions

In general, the breakdown of amygdalin into hydrocyanic acid calms down respiratory movements. This action has been attributed in animal research models to further synthesizing pulmonary surfactants. In an in vitro study, Chang et al. investigated the protective effects of amygdalin on hyperoxia-exposed type II Alveolar Epithelial Cells (AECII) isolated from premature rat lungs. Amygdalin promotes the proliferation of premature rat AECII exposed to air or hyperopia, and the best concentration of amygdalin was obtained at 200 umol/L [56].

Anti-atherosclerosis effect

Atherosclerosis refers to the buildup of fats, cholesterol, and other substances on the artery walls (plaque), that restricts blood flow [8]. Jiagang et al. evaluated the anti-atherosclerotic effects mediated by the combination of probucol and amygdalin in apolipoprotein E-knockout mice fed with a high-fat diet. The study results showed that amygdalin and probucol effectively reduced atherosclerotic progression [43]. In another animal-based study, low-density triglycerides, total cholesterol, and low-density lipoprotein were reduced in mice that received amygdalin (10 mg/kg) [57].

Improving neurodegeneration

Amygdalin is capable of treating neurological diseases and protecting nerve cell toxicity. This effect is achieved with amygdalin in doses of 0.003 to 20 mmol/L, according to Yang et al.'s study [58]. In this regard, Cheng et al.. showed that amygdalin can help treat neurological disorders such as Parkinson disease [59].

The effect of amygdalin on kidney tissue

Considering the importance of the kidneys in the secretion of excretory substances, Rajaei et al. investigated the effect of amygdalin toxicity in various concentrations on morphometric changes of kidney tissue. Their results showed that the mean weight of the kidneys, the average number, and the size of glomerular diameters changed with increasing injectable concentrations of amygdalin, but these changes were not statistically significant. The results obtained from the present study showed that amygdalin at concentrations of 25 and 50 mg/kg of body weight could not cause significant changes in the histological structure of the kidney [60]. To ensure the recovery of the dose used, further clinical studies should be performed in different amygdalin concentrations.

Effects of amygdalin on diabetes

Diabetes is one of the most common diseases of the endocrine glands, which is mainly treated with chemical methods. The traditional treatment with some herbal extracts for diabetes has been known worldwide, and it has been claimed that amygdalin accelerates the activity of pancreatic enzymes. This compound can increase insulin secretion and lower blood sugar [61]. In this regard, treatment of diabetic mice with amygdalin and almond extract significantly reduced their blood serum glucose within 4 to 8 hours after the last treatment [62].

Amygdalin and human digestive system

Benzaldehyde from the enzymatic breakdown of amygdalin plays an essential role in inhibiting the activity of pepsin and the digestion cycle. This compound was essential in improving acute gastric and atrophic diseases in mice [63]. In a study performed by Nabavizadeh et al., the role of amygdalin was investigated on alcohol-induced gastric ulcers and the possible role of nitric oxide and TNF-α in rats. They concluded that amygdalin protected gastric mucosa from alcohol-induced gastric ulcers. Images obtained from histological studies showed gastritis and ulcer formation in alcohol and amygdalin/alcohol groups, unlike in the control and alcohol/amygdalin animals (Figures 5A to 5C) [64].

The results obtained from this study showed that alcohol-induced gastric ulcer treatment with amygdalin has been successful. This gastroprotection may mediate via gastric mucosal nitric oxide production and TNF-α suppression. Another study performed by Cai et al. also showed that amygdalin has a good potential for treating patients with gastric ulcers [64].

Amygdalin nano-carriers

In a study conducted by Sohail and Abbas, the efficacy of amygdalin-loaded alginate-chitosan nanoparticles was

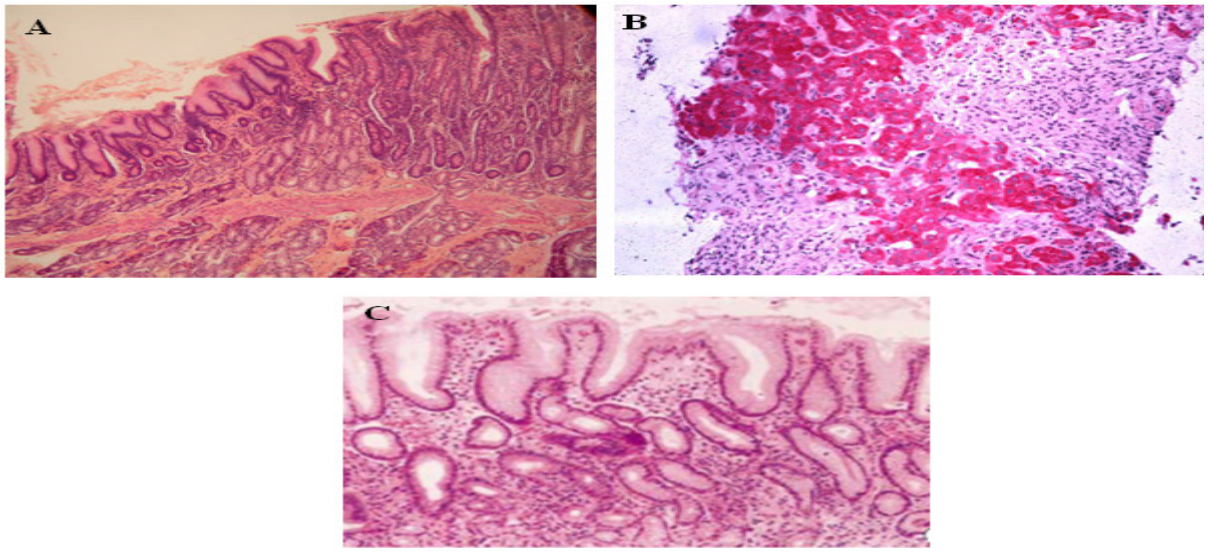

Figure 5. Histological features of gastric tissue due to amygdalin administration
A: Normal gastric mucosal (x100); B: Gastric mucosal ulcer (x100); C: Gastritis (x100). The figure was taken from reference No. 66 with permission.

investigated as biocompatible drug delivery carriers for the anticancer properties. The obtained results showed that biocompatible and biodegradable alginate-chitosan nanoparticles could be used as an effective drug delivery system for sustained and controlled amygdalin release with its improved cytotoxic effect on cancer cells without the slightest side effect on the surrounding healthy cells [27].

Discussion

As discussed earlier, amygdalin alone is not a toxic compound. Amygdalin is composed of benzaldehyde and two glucose molecules. Benzaldehyde can have analgesic and anticancer effects, while the nitrile group has antitumor properties [32, 65]. Amygdalin clinical trials have proven that its oral administration causes more toxicity than its intravenous route. The mean Lethal Dose (LD_{50}) of amygdalin was reported to be 880 mg/kg body weight by oral administration in rats. Cyanide toxicity can vary and depends on variables, such as age, obesity, dose, nutritional status, and methods of use. These variables may affect the microbial population of the gastrointestinal tract. The injection route can lead to less cyanide toxicity due to the inactivity of the β-glucosidase and rhodanese [66-69]. Research has shown that intestinal microbes cause amygdalin hydrolysis. After oral administration, intestinal microbes cause amygdalin to hydrolyze hydrogen (Figure 6).

In humans, receiving about 4 g amygdalin gradually over 15 days can cause severe poisoning. Therefore, the toxic response by the digestive system is common in all

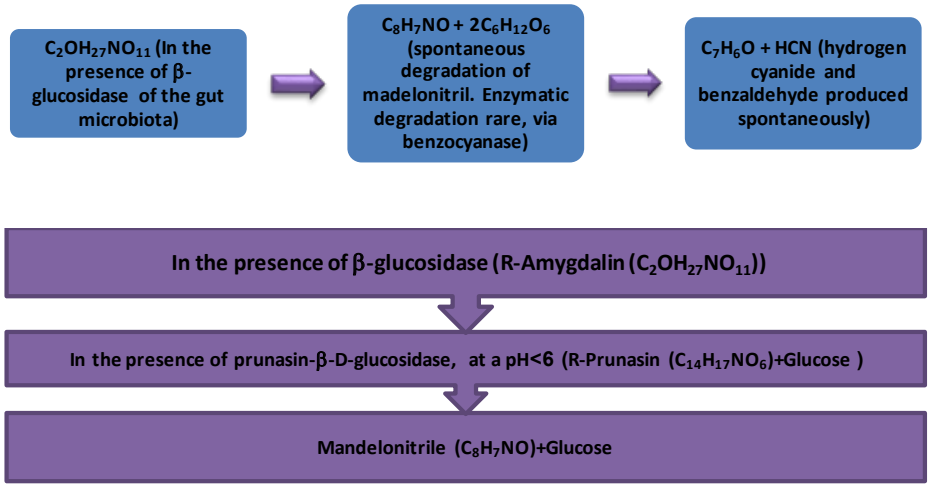

Figure 6. The pathway of amygdalin decomposition to production of hydrogen cyanide [1, 20, 75, 76]

Table 3. Reported cases of amygdalin poisoning through oral administration

Toxicity Cases	Symptoms and Effects	Ref
4 (y)	Amygdalin was fed orally, leading to severe poisoning and encephalopathy. He was recovered during three days with thiosulfate administration.	[18]
65-year-old woman with cirrhosis and hepatoma	After consuming about 3 g of bitter almonds, he went into a coma and had a drop in blood pressure. After initial treatment, the patient regained consciousness, but massive hepatic damage led to her death.	[76]
28 (month)	After consuming 10 rare seeds, he had a seizure and died after 22 days. His cyanide concentration was about 3 mg/L.	[76]
32-year-old female	Took amygdalin supplements, which caused systemic toxicity and diabetes. But he recovered with proper treatment.	[19]
28-year-old man	Consume herbal extracts with peach seed extract. He developed neuropathy due to vitamin B12 deficiency and the presence of amygdalin.	[77]
35-year-old woman	Ate 20 to 30 yellowish kernels. She suffered from the initial symptoms of poisoning. She recovered by treatment with sodium nitrite and sodium thiosulfate, followed by hydroxocobalamin.	[78]
48-year-old man	Ingested 25 g of potassium cyanide. IV administration of hydroxocobalamin aided in recovery.	[78]
23-year-old girl	Was treated with hyperbaric oxygen along with IV administration of sodium thiosulfate.	[78]

organisms. Toxic reactions in the digestive system are lost in the absence of amygdalin, and a dose of less than 1 mg orally per day is not toxic [32, 70, 71]. The intravenous injection of 6, 9, and 18 mg/kg of amygdalin increases the level of cyanide in humans' blood and can lead to a significant reduction in blood lactic acid levels [72]. The reason for this event is currently unknown. Perhaps the probable cause depends on the pathway of the amygdalin reaction or decreased activity of the lactate dehydrogenase enzyme due to a decrease in pH [73-76]. Some of the sources of amygdalin oral poisoning are listed in Table 3.

One of the problems with the use of amygdalin in reducing pain and cancer cell functions is its toxicity, especially in consumed high dosage. The results of various studies have focused more on the pharmacological and toxicological properties of amygdalin [18, 19, 77]. Evidence-based in vivo and in vitro studies are highly controversial and make amygdalin use as a therapeutic agent dangerous. These conflicting results may be related to study types. In in vitro studies, cyanoglycosides are directly delivered, whereas in in vivo studies, they are not. Studies on the mechanism of action of amygdalin on target cells and its combined effects with other drugs need more repeatability. Looking at recent sources on amygdalin, we found that many clinical trials are needed to increase the reliability of amygdalin in improving patient performance without the slightest adverse effect. In several cases, variable amounts of oral doses cause toxicity, which can be attributed to an inflammatory intestinal consortium. This outcome is because there is usually no specific way to verify each individual's microbial consortium and provide a safe oral dose in special circumstances [78].

Conclusion

In some in vitro studies, the concentration of amygdalin required to inhibit tumor growth is much lower than the concentration needed in in vivo experimental conditions. This finding may be related to the patient's clinical conditions and the effect of the dose of amygdalin and its complex mechanisms with other components. Since there is no agreement on the recommended amygdalin dosage, studies on its complex mechanism in different clinical conditions, new methods of transmission, and detoxification methods should be carefully considered in animal model studies. We hope this review provides some directions for future research and development of amygdalin use in pharmacy with the least side effect from the point of view of its possible toxicity in patient's treatments.

Ethical Considerations

Compliance with ethical guidelines

This article is a review manuscript with no human or animal sample. There were no ethical considerations to be considered in this research. This article is a review manuscript with no human or animal sample. There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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