



Review

Amygdalin in antineoplastic medicine and the relevance of nanotechnology

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Abstract

Amygdalin is a plant-based cyanogenic glycoside that has been the subject of both scientific interest and controversy for decades. Traditionally used in alternative medicine for its diverse biological activities, including anticancer, where amygdalin has been explored in complementary therapy. However, clinical utilization of amygdalin remains contentious due to concerns about its safety, primarily the release of hydrogen cyanide during its metabolism. Advancements in nanotechnology provides scope for the safe and targeted of amygdalin with improved bioavailability and targeted delivery of amygdalin, thereby, potentially eliminating the toxic effects. This review offers an update on the current research status surrounding amygdalin, with a focus on its molecular mechanisms of action, biological activities, and potential therapeutic applications. It also critically examines the challenges tied to its clinical use, particularly the safety concerns stemming from cyanide toxicity. Finally, the potential of nanotechnology in addressing cytotoxicity constraints is highlighted.

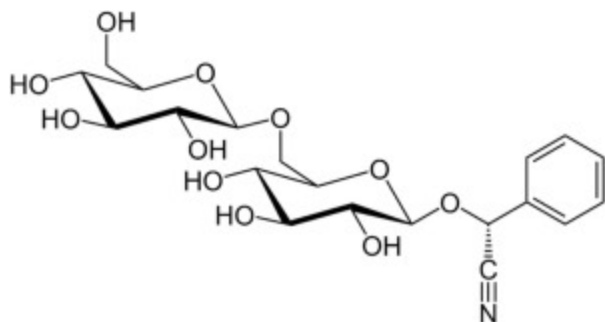


Keywords

Amygdalin; Vitamin B17; Cancer therapy; Nanomedicine

1. Introduction

Amygdalin or vitamin B17 is a naturally occurring cyanogenic glycoside that has garnered considerable attention in biomedical research due to its multifaceted biological activities. Found abundantly in the seeds of fruits such as apricots, almonds, and peaches, amygdalin has been historically utilized in traditional medicine and, more controversially, in cancer therapy. The molecular formula of amygdalin is $C_{20}H_{27}NO_{11}$ and it has a molecular weight of 457.43 g/mol [1]. Chemically, it is composed of benzaldehyde, hydrocyanic acid, and one molecule each of D-mannitol- β -d-glucoside-6- β -glucoside linked by glycosidic bond [2] (Fig. 1).



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Fig. 1. Chemical structure of amygdalin [2].

It is known for its potential therapeutic properties, including anti-inflammatory [3], antioxidant [4], and immunomodulatory effects [5], in addition to its purported anticancer activity [6]. However, the use of amygdalin, particularly in the form of laetrile [7] (d-Mandelonitrile- β -glucuronide), which is amygdaline devoid of the terminal sugar moiety, has been a subject of significant debate within the scientific community due to its associated toxicity risks, primarily from the liberation of cyanide during hydrolysis. However, recent advancements in nanotechnology have opened new avenues for the

exploration of amygdalin as a formidable therapeutic agent, particularly in cancer treatment. Nanoparticle formulations of amygdalin have been reported to enhance its bioavailability, with the possibility of targeted delivery to cancer tissue, thereby mitigating its toxic effects. Despite the potential benefits observed in preclinical studies, the clinical application of amygdalin remains contentious, with a lack of robust evidence from well-designed clinical trials to support its safety and therapeutic effectiveness. This review aims to provide a comprehensive overview of the current research involving amygdalin, focusing on its biological activities, potential therapeutic applications, particularly in cancer therapy, and the challenges associated with its clinical use and opportunities available, especially through use of nanotechnology in the deployment of the same. This work is also anchored around the need for further research to provide a better scope of understanding the therapeutic potential and safety profile of amygdalin, especially when deployed in nanoformulation.

2. Bioactive profile of amygdalin

Amygdalin demonstrates a wide array of biological activities, including immunomodulatory, antioxidant, anti-inflammatory, and antimicrobial effects. Extensive research underscores its significant impact across various medical conditions. This diverse activity is expected due to its pivotal role in cellular and molecular signaling and its involvement in several critical signaling pathways.

2.1. Biological activities of amygdalin

2.1.1. Anti-tumor activity of amygdalin

Amygdalin was used as a combinational drug in cancer therapy since the early 1970s [5]. Despite the known toxicity of amygdalin, a number of studies have shown that treatment with an optimal dose unleashes the desired anti-cancer properties of the compound [8], [9], [10], [11], [12].

For example, one study [13] examined the effect of amygdalin on apoptotic proteins like Bax and Bcl-2 in breast cancer and the results were indeed promising in the light of the application of amygdalin in the treatment of HER2 positive breast cancer. Another study investigated the combined use of amygdalin and the anticancer drug Sorafenib, reporting a reduction in tumor burden and hepatic damage [14] Similar studies on prostate [15] (LNCaP and DU145) and cervical [16] cancer cells (HeLa) reported the increased expression of apoptotic proteins Bax and caspase-3 and decreased expression of Bcl-2 and the

induction of apoptosis via the endogenous mitochondrial pathway respectively. Interestingly, amygdalin was also found to disrupt the expression of anti-apoptotic genes like the XIAP and Survivin [17]. In another study [18] the cancer-inhibiting potential of amygdalin was evaluated through the depiction of oxidative stress on breast cancer cells. This study concluded that amygdalin was highly potent in reducing the growth of breast cancer cells in a dose and time-dependent manner. In addition, the ability of amygdalin to induce cell cycle arrest and thereby disrupt cell proliferation in cancer cells has been reported in various studies [19], [20], [21]. Furthermore, in colorectal cancer cells (SNU-C4), amygdalin treatment was found to induce significant differences in gene expression [22]. According to this study, amygdalin was found to be involved in the downregulation of genes involved in the cell cycle regulation, and therefore permitted the inhibition of tumor cell proliferation. Moreover, another study [9] on metastatic non-small-cell lung cancer demonstrated that amygdalin was extremely potent in inhibiting the proliferative, invasive and migratory potentials of the tumor cells. Intriguingly, this study also identified that amygdalin intricately supported the upregulation of proteins involved in cancer cell metastasis. Yet another study [23] reported that amygdalin was able to decrease the chemotactic and invasive abilities of renal carcinoma cells. Interestingly however, amygdalin was found to be comparatively more effective in prostate and cervical cancer than other cancers because of its effectiveness at comparatively lower doses at limiting and inhibiting the division of cancer cells [8], [9], [24], [25]. Moreover, amygdalin also serves as a prodrug for antibody-directed enzyme prodrug therapy for bladder cancer [26], [27]. Activation of the amygdalin at the site of the tumor could efficiently kill tumor cells whilst also decreasing the toxicity and the side-effects from traditional chemotherapies.

Interestingly, the combination of amygdalin and β -glucosidase has demonstrated promising potential in cancer treatment [28]. For example, studies have evaluated the therapeutic effects of specific β -glucosidase activators in combination with amygdalin in mice with implanted tumors [29]. In addition, cancer cell surface antigens are also known to be targeted by β -glucosidase using antibodies when the combination is administered intravenously. In this light, amygdalin, functioning as a prodrug, is activated by β -glucosidase and binds to the tumor's target site, enabling its destruction. Additionally, the binding of cell membrane peptides to β -glucosidase enhances the enzyme's penetration into capillary endothelial cells and deep extracellular solid tumors, ultimately leading to tumor cell death [30].

2.1.2. Immunomodulatory activity of amygdalin

Amygdalin modulates the immune system and is known to participate in improving immune function through the inhibition of Transforming Growth Factor-beta 1 (TGF- β) and the section Interferon gamma (IFN- γ) and Interleukin 2 (IL-2) [5]. In addition, amygdalin also regulate the expression of T-lymphocytes, wherein, low doses were able to induce the inhibition of immune cell proliferation [5]. Moreover, in various other reports, similar doses were able to decrease immune-suppression in kidney transplantation experiments in mouse models [31], [32]. Therefore, although amygdalin may increase the efficiency of immune cells, other studies have reported that it has enhanced the success of organ transplantation [33], [34]. Thus, further research is required for reconciling such opposing immunomodulatory mechanisms elicited by amygdalin.

2.1.3. Anti-inflammatory activity of amygdalin and role in pain-relief

Inflammation plays a central role in a wide range of human diseases including cancer [35]. Amygdalin has been linked to the reduction of inflammation through the inhibition of nitrite oxide synthesis and inhibition of prostaglandins. In particular, a study reported the anti-inflammatory potential of amygdalin in an arthritic rat model [3]. Similarly, another study identified that low doses of amygdalin affected the expression of inflammatory cytokines like Tumor Necrosis Factor- α (TNF- α) and Interleukin-1 β (IL-1 β) thereby leading to a reduction in formalin-induced pain in mice models [36], as similarly observed in another study in mice models [25].

2.1.4. Antioxidant activity of amygdalin

Amygdalin displays potent antioxidant activity as reported in several studies [37], [38], [39]. In one study carried out on mice models, amygdalin was found to exhibit antioxidant activity in liver tissue, which suppressed tunicamycin-induced endoplasmic reticulum stress [40]. Furthermore, the antioxidant activity of amygdalin against cervical cancer cells was found to be particularly significant [4].

2.1.5. Antibacterial activity of amygdalin

Evidence supporting the antibacterial activity of amygdalin is rare. However, there is evidence of antibacterial effects of amygdalin extracted from apricot kernels [41], whereby the susceptibility of various strains of pathogenic bacteria including *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Serratia marcescens* on varying concentrations of amygdalin was ascertained. In addition, a certain report highlighted that amygdalin possesses remarkable antimicrobial activity against a wide range of pathogens, including Gram-positive and Gram-negative bacteria, as well as various fungal isolates,

underscoring its broad-spectrum antimicrobial potential [42]. However, further and more in-depth studies are necessary for the establishment the scope of effectiveness on a variety of bacteria species as well as the mechanistic pharmacology involved.

2.1.6. Anti-atherosclerosis activity

Atherosclerosis is a condition depicted by the build-up of cholesterol and fats along the walls of the arteries and major blood vessels that eventually restricts the flow of blood through the arteries [1]. Used in combination with probucol, amygdalin was found to impede the progression of atherosclerosis in mice [34]. Furthermore, mice dosed with amygdalin were found to have lower levels of cholesterol, low-density lipoproteins, and low-density triglycerides [43].

2.1.7. Anti-fibrosis activity of amygdalin

The inhibitory effect of amygdalin on fibrosis has been documented by various studies on renal, liver, pancreatic, and pulmonary fibrosis [44], [45]. In particular, a certain study revealed that hepatic fibrosis-related genes were expressed at significantly lower levels in amygdalin-treated groups compared to control groups [46]. This finding suggests that amygdalin may serve as a promising candidate for the prevention and treatment of hepatic fibrosis, as it appears to mitigate the genetic expression patterns associated with the progression of this disease. Moreover, the anti-fibrotic potential of amygdalin was further evidenced in research focused on idiopathic pulmonary fibrosis, a chronic and often fatal lung disease characterized by progressive scarring of lung tissue. This study evaluated the cytotoxicity of amygdalin epimers—L-amygdalin and D-amygdalin—in both in-vitro cell models and in-vivo mice models of idiopathic pulmonary fibrosis [47]. The results indicated that L-amygdalin exhibited a higher cytotoxic potential in cell models, suggesting it may be effective at targeting and eliminating diseased cells in a controlled environment. However, when tested in mice models, D-amygdalin proved to be more effective in combating pulmonary fibrosis [47]. Moreover, D-amygdalin demonstrated a stronger inhibitory effect on inflammation compared to L-amygdalin and showed comparable efficacy in suppressing the mRNA and protein expression levels of fibrosis-related biomarkers, indicating its potential for reducing the fibrotic processes that underlie idiopathic pulmonary fibrosis [47].

In a similar vein, another study underscored amygdalin's potency in improving the metabolomics profile of rats with bleomycin-induced pulmonary fibrosis, a commonly used model to mimic human pulmonary fibrosis in research [48]. This study found that amygdalin not only exerted anti-fibrotic effects but also positively influenced the

metabolomics activity in PF rats, altering metabolic pathways that could be key to understanding and treating the disease [48]. These findings provide valuable experimental evidence supporting the potential clinical application of amygdalin in treating fibrosis, offering a foundation for future research and possible therapeutic development.

Taken together, these studies highlight the multi-faceted role of amygdalin in fibrosis prevention and treatment, demonstrating its impact at both the genetic and metabolic levels in different models of fibrosis. The insights gained from this research could pave the way for the development of novel amygdalin-based therapies for a variety of fibrotic diseases.

2.1.8. Anti-neurodegeneration activity of amygdalin

Amygdalin has been shown to protect against nerve cell toxicity, which usually progresses into neurological diseases [49]. In this regard, amygdalin has the potential for use in treating neurological diseases [50]. Significantly, amygdalin has been reported to present positive outcomes when used in Parkinson's disease [51].

2.1.9. Activity of amygdalin on diabetes

Amygdalin enhances pancreatic enzyme secretion, whereby the secretion of insulin and subsequent reduction in blood sugar levels was reported [52]. Furthermore, a combinatorial treatment of diabetic mice involving almond extract with amygdalin significantly reduced blood glucose levels [52].

2.1.10. Activity of amygdalin in the digestive system

Amygdalin is enzymatically hydrolyzed into glucose, benzaldehyde and hydrocyanic acid. Benzaldehyde in turn inhibits the enzymatic activity of pepsin, which is crucial in digestive enzymatic cascade. In concert with this, amygdalin was found to improve acute gastric diseases in mice models [53]. Similarly, amygdalin protects the gastric mucosa from alcohol induced ulcers, thereby helping to alleviate the symptoms of acute gastric diseases in rat models [54]. These findings were further supported by another study, which reported that amygdalin was effective in treating alcohol-induced gastric ulcers [55]. Another noteworthy effect of amygdalin in the digestive system is its capacity to modulate the gut microbiota [56]. Research has indicated that cyanide levels in the body are influenced by various factors, including the composition of gut bacteria [57]. Specifically, gram-negative *Bacteroides* exhibit high glucosidase activity, releasing cyanide during the symbiotic digestion of amygdalin. While antibiotics can reduce gut flora, studies show that

administering amygdalin in such conditions leads to the detection of prunasin but no HCN. This indicates that amygdalin is metabolized by intestinal enzymes solely into prunasin, which is subsequently transported to the colon and fully digested by microbial β -glucosidase [58]. Probiotic therapy may offer an additional approach, as probiotics have been shown to reduce *Bacteroides* levels. However, it is already well-established that *Lactobacillus* produces β -glucosidases. Further research is needed to evaluate HCN levels in cancer patients consuming a diet low in *Bacteroides* but enriched with β -glucosidase-producing *Lactobacillus* [56].

2.1.11. Activity of amygdalin in improving respiratory conditions

The hydrolysis of amygdalin into hydrocyanic acid elicits a calming effect on respiration, due to a protective effect on type II alveolar epithelial cells exposed to air or hyperopia and the promotion of proliferation of these cells, as observed in rat models [25].

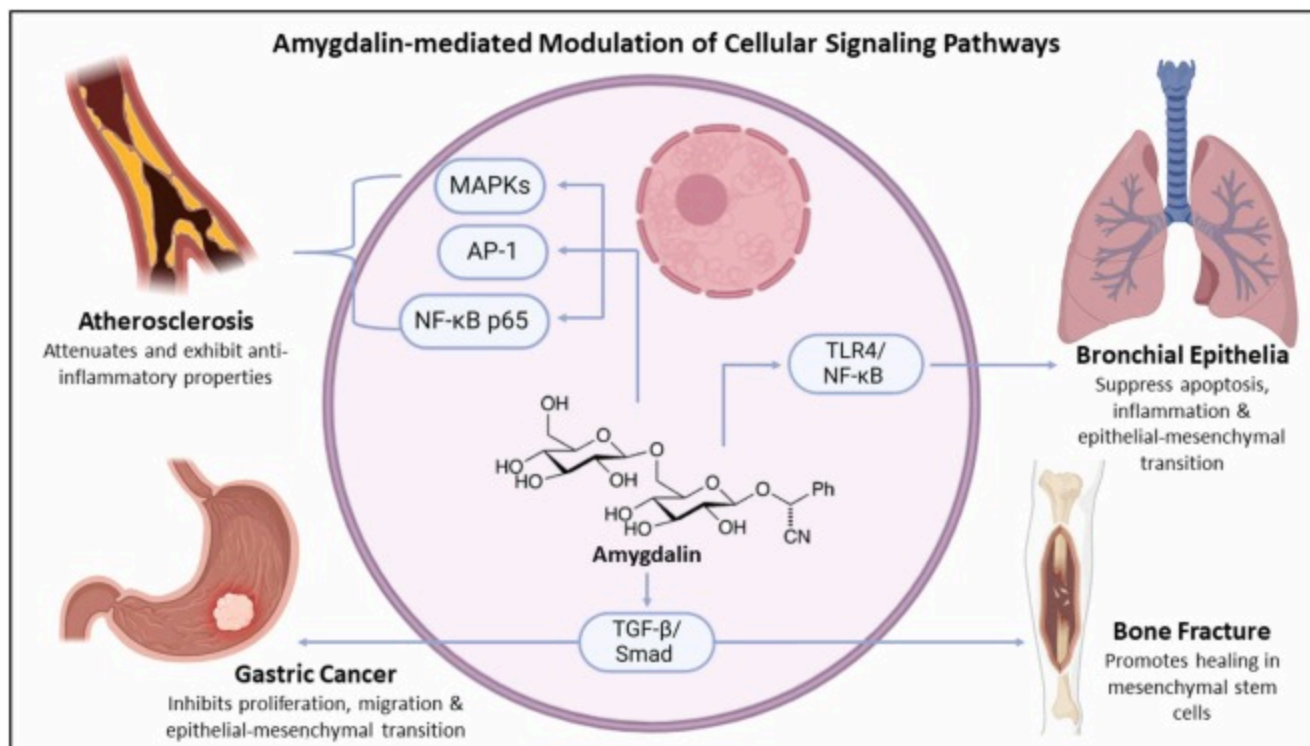
Table 1. A summary of the Bioactive profile of Amygdalin and its implications in human physiology and diseases.

Biological Activity	Implications	References
Anti-Tumor Activity	- Effective in reducing growth and metastasis: Increases apoptotic proteins (e.g., Bax, caspase-3) and decreases anti-apoptotic proteins (e.g., Bcl-2) in various cancers.	[1], [5], [7], [8], [9], [10], [11], [13], [15], [16], [21], [22], [23], [24], [25]
	- Found to enhance bioavailability and enable targeted delivery to cancer tissues, thereby reducing toxic effects.	[59]
Immunomodulatory Activity	- Modulates immune function by inhibiting TGF- β and enhancing IFN- γ and IL-2 secretion.	[5], [31], [32], [33], [34]
	- Affects T-lymphocyte regulation, potentially enhancing or inhibiting immune response.	
	- Shown to enhance organ transplantation success in mouse models.	
Anti-inflammatory Activity	- Reduces inflammation by inhibiting nitric oxide synthesis and prostaglandins.	[3], [25], [36]
	- Decreases inflammatory cytokines (e.g., TNF- α , IL-1 β) and provides pain relief in arthritis and	

Biological Activity	Implications	References
	other inflammatory conditions.	
Antioxidant Activity	<ul style="list-style-type: none"> - Exhibits potent antioxidant effects, especially in liver and cervical cancer cells. - Suppresses endoplasmic reticulum stress in liver tissues. 	[4] , [37] , [38] , [40]
Antibacterial Activity	<ul style="list-style-type: none"> - Limited evidence, but shown to possess antibacterial properties against strains like <i>Streptococcus Pyogenes</i>, <i>Pseudomonas aeruginosa</i>, and <i>Staphylococcus aureus</i>. 	[41]
	<ul style="list-style-type: none"> - Demonstrated broad-spectrum antimicrobial activity against Gram-positive, Gram-negative bacteria, as well as various fungal isolates. 	[42]
Anti-atherosclerosis Activity	<ul style="list-style-type: none"> - Reduces atherosclerosis progression in combination with probucol. - Lowers cholesterol, LDL, and triglycerides in mice. 	[1] , [43]
Anti-fibrosis Activity	<ul style="list-style-type: none"> - Inhibits fibrosis in various organs, including kidney, liver, pancreas, and lungs. 	[44] , [45] , [46] , [47] , [48]
Anti-neurodegeneration Activity	<ul style="list-style-type: none"> - Protects nerve cells and shows potential in treating neurological diseases like Parkinson's. 	[49] , [50] , [51]
Activity on Diabetes	<ul style="list-style-type: none"> - Enhances pancreatic enzyme activity, increases insulin secretion, and lowers blood glucose levels. 	[52]
Digestive System Activity	<ul style="list-style-type: none"> - Improves acute gastric conditions and protects against alcohol-induced ulcers. - Benzaldehyde component inhibits pepsin activity. 	[53] , [54] , [55]
Respiratory Conditions	<ul style="list-style-type: none"> - Provides a calming effect on respiration and protects alveolar cells from hyperoxia-induced damage. 	[25]

2.2. Amygdalin in cellular signaling

Amygdalin has long been studied for its modulatory effects on cellular signaling pathways. Research has shown that it influences various physiological processes through both extra- and intracellular signaling pathways, impacting secretory activity, cell viability, steroidogenesis, proliferation, and apoptosis [60]. It is interesting to note that the biosynthesis of amygdalin involves cytochrome P450 (CYP) such as PdCYP79D16 and PdCYP71AN24 [61], [62]. Thus, it is unsurprising that amygdalin is also responsible in the modulation of several other CYP type or related enzymes in humans. Moreover, amygdalin has demonstrated potential therapeutic modulatory effects in various diseases as highlighted earlier. In the current context for example, amygdalin attenuates atherosclerosis and exhibits anti-inflammatory properties through modulation of MAPKs, AP-1, and NF- κ B p65 signaling pathways [63]. Modulatory effects in the inhibition of certain cancers, particularly gastric cancer is also exhibited by amygdalin, whereby the proliferation, migration, and epithelial-mesenchymal transition of gastric cancer cells is effected by suppression of the TGF- β /Smad signaling pathway [64]. Additionally, amygdalin has been implicated in promoting fracture healing through the TGF- β /Smad signaling pathway in mesenchymal stem cells [65]. Apoptosis of the airway epithelium is suppressed by amygdalin in addition to the suppression of inflammation, and epithelial-mesenchymal transitioning via restraining the TLR4/NF- κ B signaling pathway in bronchial epithelial cells [66]. Evidently, amygdalin's role in cellular signaling affects a broad spectrum of biological processes and diseases, underscoring its potential for therapeutic applications in biomedical research (Fig. 2). Further exploration of the mechanisms underlying amygdalin's actions on cellular signaling pathways could provide valuable insights for future therapeutic developments.



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Fig. 2. An illustration of amygdalin's role in modulating cellular signaling pathways and its effects on human pathogenesis.

3. Amygdalin in cancer therapy

Cancers are multi-factorial diseases that are caused by a variety of intrinsic and extrinsic factors [67], [68], [69], including microorganisms and viruses [70], [71], [72], [73], [74], [75], [76], [77], [78]. Advancements in cancer therapies have revolutionized treatment options, introducing groundbreaking innovations such as precision medicine, immunotherapies, and nanomedicine [79]. In this context, amygdalin has emerged as a particularly promising candidate, given its demonstrable potential in anti-cancer activity. Here we discuss the latest advancements in the application of amygdalin for cancer treatment and the impact of nanomedicine within this framework, while also evaluating its clinical impact.

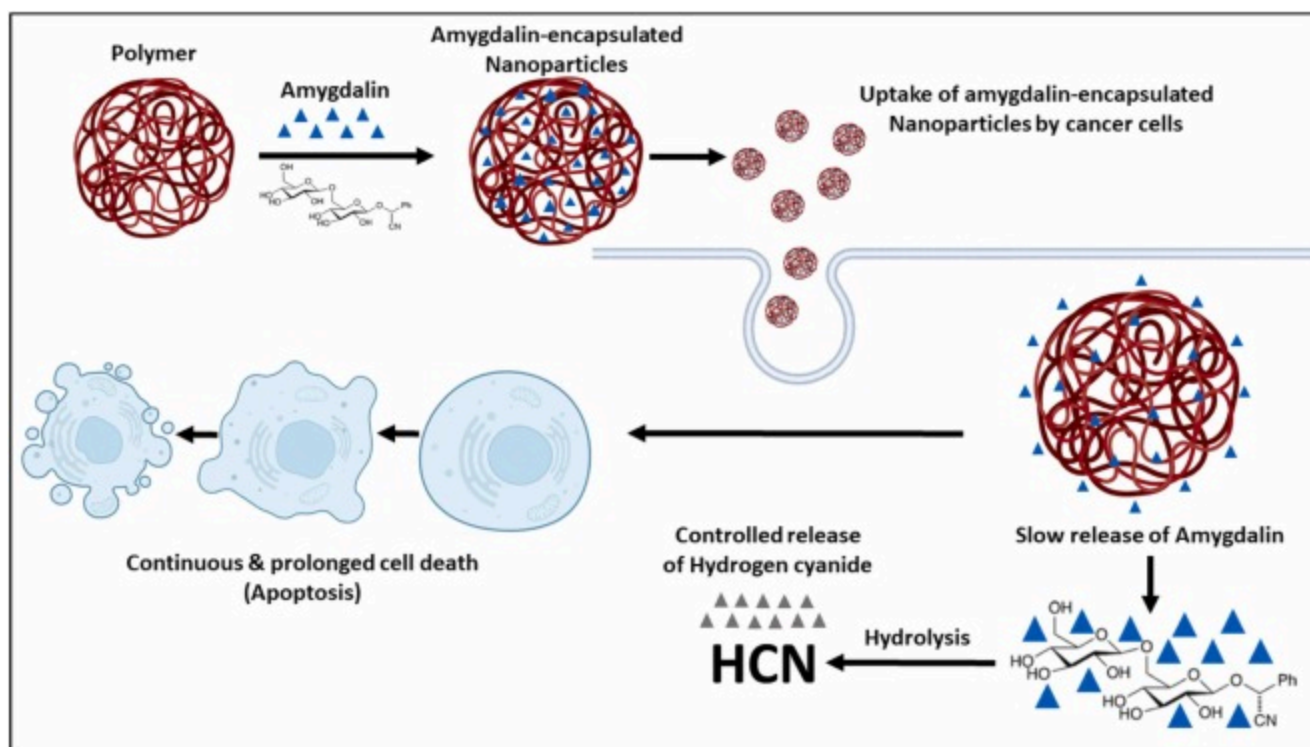
3.1. Role of amygdalin in cancer nanomedicine

Amygdalin has been explored for its potential therapeutic effects across a range of diseases. One promising approach involves encapsulating it in nanoparticulate delivery systems, which addresses some of the toxicity concerns, but also potentiates uptake into cells. Nanoparticulate delivery systems are submicron in dimension and fabricated with various

types of materials, particularly polymers. They are versatile and have proved invaluable in deploying poorly soluble or absorbable drugs to where needed. They can be formulated to ensure a controlled release of the therapeutic cargo [80], [81]. Amygdalin, has attracted attention in the field of nanomedicine due to its aforementioned therapeutic applications and qualifies for nano-encapsulation due to the huge therapeutic potential this could entail [79], [82] (Fig. 2). Recent studies have explored the application of amygdalin in nano-formulations, particularly in breast cancer therapy. For example, the use of a pH-sensitive multifunctional nano-core-shell composite containing amygdalin for effective localized breast cancer therapy aimed at evaluating its efficacy modulating tumor-promoting factors and enhancing the effects of radiotherapy on cancer cells [83]. Moreover, the functionalization of carbon quantum dots with amygdalin has been explored for its potential in cancer diagnosis and therapy, showcasing the versatility of nanotechnology in cancer treatment [84]. Additionally, Amygdalin-based, gold/silver nano-drug delivery systems exhibited controlled release of amygdalin, enhancing its cytotoxic effects on cancer cells [11], [85], [86]. Likewise, nanoparticle-based amygdalin formulations, were shown to enhance bioavailability and enable targeted delivery to cancer tissues, thereby reducing toxic effects [59]. Combination therapies utilizing amygdalin with conventional chemotherapeutic agents have been explored to enhance treatment efficacy and reduce toxicity [87]. Such combinations provide scope for the utilization of amygdalin in low concentrations and thereby allaying any toxicity concerns. In this regard, a folic acid derivative of amygdalin encapsulated in nanoparticles was evaluated on breast cancer cells by focusing on the radio-sensitizer efficacy of these nanoparticles on specific cancer cell lines [88]. The results indicated that amygdalin-folic acid nanoparticles inhibited cancer cell proliferation and enhanced the effects of radiotherapy through the modulation of tumor-promoting factors and immunosuppressive modulators. Furthermore, novel therapeutic regimens encapsulating with cisplatin and vitamin D3 with amygdalin have shown synergistic effects against lung cancer [89].

These studies emphasize the promising potential of nanoencapsulation of amygdalin, alone or in combination with other therapeutics as an effective approach, in the deployment to relevant tissues and the treatment of various diseases, particularly cancer. The development of nano-formulations containing amygdalin has the potential to improve the efficacy of existing therapies and addresses the existing challenges associated with cancer treatment. However, despite the success of such findings, the efficacy of amygdalin in several diseases including cancer, clearly more studies are warranted, especially in the realm of nanoencapsulation, due to the huge potential this approach holds.

Further, the safety profile of amygdalin, particularly in nanoparticle form, is another critical aspect of its potential application in cancer therapy. Studies have indicated that while amygdalin can release HCN upon metabolism, the controlled release through nanoparticles can mitigate this risk, allowing for safer therapeutic use [90]. Furthermore, research has shown that amygdalin can exert genotoxic effects at high concentrations, necessitating careful consideration of dosing regimens when developing nanoparticle formulations [91].



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Fig. 3. An illustration of deployment of HCN from nanoparticle after cellular uptake.

Table 2. An overview of the nanotechnology-based approaches involving amygdalin for cancer treatment.

Amygdalin-based Drug Nano-formulations	Description	Function
pH-sensitive Nano-core-shell Composites	Developed for localized breast cancer therapy.	These composites release amygdalin in response to the acidic environment of tumors, improving the effectiveness of radiotherapy [83].

Amygdalin-based Drug Nano-formulations	Description	Function
Amygdalin-folic acid Nanoparticles	Developed to target breast cancer cells.	Leverages the overexpression of folic acid receptors, effectively inhibiting cell proliferation and enhancing the effects of radiotherapy [88].
Amygdalin and Cisplatin-loaded Nanoparticles	Developed for the treatment of lung cancer.	Combined with cisplatin and vitamin D3, these nanoparticles show synergistic effects in treating cancer, helping to overcome drug resistance [89].
Amygdalin-based Nano-drug Delivery Systems	Chitosan-based/gold/silver nanoparticles may be used as an effective drug delivery system for amygdalin. Amygdalin-loaded niosomes (ALN) were integrated into a carbopol gel formulation to develop a drug delivery system to evaluate the selectivity, efficacy, and toxicity of amygdalin <i>in-vivo</i> .	These systems demonstrate sustained and controlled release of amygdalin, enhancing its cytotoxic effects on cancer cells [11], [85], [86]. Nnanoparticle-based amygdalin formulation was shown to enhance bioavailability and enable targeted delivery to cancer tissues, thereby reducing toxic effects [59].

3.2. Clinical relevance of amygdalin-based anticancer therapeutics

The anti-cancer effects of amygdalin have been demonstrated in *in-vitro* and animal models. However, evidence depicting *in-vivo* data in humans is still scarce. The first study on the efficacy of amygdalin was carried out in 1978 on 93 cancer patients [92]. However, this study did not draw sufficient conclusions in support of the cancer-inhibiting potential of amygdalin. A subsequent study conducted in 1982 to assess the efficacy of amygdalin on 178 cancer patients [93] also indicated that amygdalin did not serve any major therapeutic advantage towards limiting or inhibiting carcinogenesis, correcting symptoms, or increasing survival time. Evidently, both studies were largely unsuccessful in exhibiting the anti-tumor activities based on the *in-vitro* studies. However, according to another report [94], the inconclusiveness of these studies can be attributable to flaws in their design and also the were based on small sample sizes. Crucially, the study did not include a control group and

thus the reliability of the results may be in question. On the whole, both studies were retrospective and lacking in data completeness.

Promisingly, a more recent study on six patients with advanced cancer, presented minor clinical side effects during treatment with amygdalin, however, there was an increase (up to 2.1 mg/ml) in the level of cyanide in the blood of subjects on oral doses of amygdalin was observed [95]. According to this study, amygdalin was excreted unchanged in the urine.

To date no high-quality randomized control trials have been conducted to evaluate the anti-cancer properties of amygdalin; thus, giving rise to a huge gap and opportunities in this regard. Consequently, the Cochrane Collaboration concluded that there is no sound data from controlled clinical trials supporting the claim that amygdalin has beneficial effects for cancer patients [96]. Moreover, the Food and Drug Administration (FDA) has banned the sale of amygdalin as a medicinal product due to concerns about cyanide toxicity [97]. Whilst ongoing research point to the therapeutic potential of amygdalin, particularly in cancer treatment and other conditions, the lack of robust evidence from controlled clinical trials has meant that questions about its efficacy and safety lingers. Thus, further well-designed studies are warranted to clarify the role of amygdalin in medical practice and to address its toxicity and potential side effects. Nanoencapsulation of amygdalin provides an avenue for its deployment in a manner that harnesses its full potential and also addressing the aforementioned side effects. This intern, will pave the way for meaningful clinical exploration because thus far, all clinical studies have relied on the use of amygdalin in its nascent form or in conventional dosage forms.

4. Amygdalin toxicity: challenges and future considerations

The toxicity of amygdalin has been a subject of interest due to its potential health implications. Amygdalin is widely classified as a cyanogenic glycoside [90]. Studies have shown that amygdalin can induce toxicity, especially when consumed orally, as it can lead to the production of hydrogen cyanide in the gastrointestinal tract [98]. The toxicity of amygdalin has been demonstrated in various animal studies, indicating that high doses of amygdalin can have adverse effects on health [60]. Upon oral ingestion, amygdalin undergoes enzymatic cleavage by amygdalin lyase, resulting in the formation of prunasin and glucose. Prunasin is then further hydrolyzed by the enzyme prunasin lyase, producing mandelonitrile and glucose. Mandelonitrile is subsequently broken down into benzaldehyde and hydrogen cyanide (HCN) through the catalytic action of hydroxyl nitrile lyase [99]. The release of cyanide is particularly hazardous, as it interferes with cellular respiration by binding to cytochrome oxidase, a critical enzyme in the electron transport chain. The

dissociation of hydrocyanic acid into cyanide ions allows for their absorption into the body, where they disrupt the electron transfer process within the respiratory chain, effectively blocking the utilization of oxygen. This interference results in cellular hypoxia and lactic acidosis, making the toxicity of amygdalin potentially lethal [100]. Interestingly, a certain study [101] observed the metabolism of orally administered amygdalin in a simulated gastrointestinal cell culture and found that it degraded first to prunazine and later to mandelonitrile by β -glucosidase, then hydroxylated to hydroxymandelonitrile in the small intestine. No cyanide or benzaldehyde was released at this stage, indicating that cyanide is likely to be produced in the lower intestine, which is rich in bacterial microflora. Firmicutes, Bacteroidetes, and Actinobacteria are the main groups of bacteria that contribute to the release of cyanide in the gut. Lethal oral doses for cyanide are 2.13–6 mg.kg⁻¹ body weight, and it has been confirmed that 59 mg of cyanide is released from 1 g of amygdalin [102]. However, based on other reports [103], highly purified amygdalin applied at “therapeutic” concentrations (orally 0.6–1 g.kg⁻¹) is unlikely to cause toxicity [104].

In essence, amygdalin is known to influence multiple cellular signalling pathways. It activates p38MAPK, which modulates death stimuli, promotes the activation of apoptotic proteins like Bax, and inhibits anti-apoptotic proteins like Bcl-2. This activation leads to mitochondrial outer membrane permeabilization, a critical event that facilitates the release of cytochrome c. Additionally, amygdalin promotes the overproduction of reactive oxygen species (ROS), disrupting oxidative balance and further contributing to apoptosis [60].

However, many studies have highlighted that the toxicity of amygdalin is markedly reduced when administered via routes other than oral ingestion. Acute toxicity experiments have revealed that oral administration is approximately 40 times more toxic than intravenous injection [105]. For example, research has demonstrated that an intravenous injection of amygdalin at a dose of 500 mg/kg caused no fatalities in experimental animals, whereas the same dose delivered intragastrically resulted in an 80 % mortality rate within just 48 h [106].

Moreover, a particular study noted that amygdalin on its own did not exhibit toxicity after a 24-hour incubation period. However, it showed significant cytotoxic effects—such as the inhibition of cell proliferation, generation of reactive oxygen species (ROS), and induction of apoptosis, only following treatment with β -glucosidase. Thus, amygdalin carries a significant risk, particularly when administered orally [107], because cyanide is released in much larger quantities after oral ingestion compared to intravenous administration. This increased cyanide release is attributed not only to the rapid activity of intestinal microflora [108] but also to the mechanical breakdown of amygdalin through chewing [109].

Whilst amygdalin has been explored for its potential anticancer properties, it is crucial to consider its toxicity profile and how this can be harnessed for potential therapeutics. Amygdalin induces toxicity in a dose-dependent manner, with high doses leading to negative effects on oxidative balance and histopathology in animal models [60]. Furthermore, the conversion of amygdalin to cyanide in the gut highlights the potential risks associated with its consumption, emphasizing the importance of understanding its toxicokinetics [99]. Studies have shown that amygdalin can be enzymatically converted to cyanide, which can have detrimental effects on various physiological processes [110]. However, such toxicity in humans is imposed only on overconsumption of amygdalin [111]. Therefore, careful regulation of amygdalin use in therapeutic applications may be the way forward toward effective therapeutic outcome. In addition, there is a huge scope for the application of nanoformulation to address the toxicity concerns highlighted above.

5. Conclusion

Amygdalin displays a wide range of biological activities, including immunomodulatory, anti-inflammatory, antioxidant, antibacterial, and anti-fibrotic effects, as well as its influence on digestive system function and modulation of gut microbiota. These multifaceted properties underscore its significant potential as a powerful therapeutic agent for various diseases, including cancer, diabetes, atherosclerosis, neurodegenerative disorders, and respiratory conditions. However, current evidence from clinical studies is insufficient to conclusively support the widespread use of amygdalin in medical practice in cancer therapy. The potential risks associated with cyanide toxicity necessitate careful consideration and further investigation through well-designed clinical trials. Notwithstanding, it is the view of the authors that the usefulness of amygdalin can best be harnessed when encapsulated, especially as nanoparticulate delivery systems. This approach permits the controlled release of amygdalin and also permits targeting to relevant parts of the body, for example in tumors. Thus, exploration of amygdalin in nanoparticulate platforms presents promising possibilities for enhancing its efficacy and minimizing its toxicity, which has been a major concern in its traditional use. The continued exploration of amygdalin in nanomedicine and its integration into comprehensive cancer treatment strategies may offer new opportunities for improving patient outcomes, provided that safety concerns are adequately addressed.

CRedit authorship contribution statement

Nashiru Billa: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Queenie Fernandez:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NASHIRU BILLA reports financial support and article publishing charges were provided by Qatar National Library. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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