Amigdalin

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REVIEW ARTICLE

Amygdalin as a Potential Anti-Cancer Agent: A Concise Review of Therapeutic Insights and Mechanisms

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ABSTRACT

Amygdalin, also known as laetrile, has generated significant controversy within the scientific medical community regarding its efficacy as a cancer treatment. Extracted primarily from the seeds of fruits like apricots and almonds, it has been promoted by certain groups as a potential cure for cancer despite criticism regarding its toxicity and minimal therapeutic value. This review aims to analyze the available literature on amygdalin, focusing on its chemical characteristics, proposed mechanisms of action, and its role in cancer prevention and therapy. A comprehensive review of preclinical data and clinical trials was conducted to assess amygdalin's potential effects and associated risks. The analysis of existing studies provides insights into the complexity of amygdalin's biological activity, including its interactions and suggested pathways in cancer treatment, while highlighting the need for further research to clarify its efficacy and safety. Ultimately, the review contributes to the ongoing discussion surrounding amygdalin's position in oncology and emphasizes the necessity for continued exploration to develop effective cancer treatment strategies.

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INTRODUCTION

Amygdalin is a substance whose existence is often contended. It is not recognized as a vitamin because it does not support human life[1]. This is a crucial point to understand before delving into the research of amygdalin. The first isolated and concentrated form of amygdalin was created by Dr. Ernst T Krebs Jr., who called the purified form laetrile. He based his theory on cancer as a deficiency of certain nutrients and vitamins, one of which is amygdalin[2]. His new theory was termed the trophoblast theory. In short, Krebs believed that the growth of cancer was a result of embryonic or trophoblastic cells, which did not receive certain micro-nutrients to develop into normal body cells[2]. Modern research has not supported this theory;

however, many still believe it to be true and maintain that amygdalin /laetrile effectively thwarts cancer growth by "targeting" and killing harmful cells[2]. Amygdalin has been highly acclaimed as an anti-cancer agent. Laetrile, a purified form of amygdalin, was initially used in cancer therapy as early as 1845. [3] It was not until the 1970s that this natural substance was highly promoted in the public; however, its use has become highly controversial[4]. In more recent years, there has been increased interest and use from cancer patients seeking alternative and natural remedies[5]. Unfortunately, many of these patients and advocates of amygdalin therapy are not fully educated on the history, biochemistry, and potential therapeutic benefits and risks of this very polarizing natural substance[5]. This paper aims to consolidate the many varied opinions of amygdalin in a balanced, evidence-based, and objective manner. Ultimately, the goal is to enhance public awareness of amygdalin so patients can make the most informed treatment decisions.

Background on Amygdalin

Previous theories on amygdalin have declared that it is an amygdalin, a beta glucoside obtained from apricot pits, and an anti-cancer agent, as shown in Figure 1. [7] This theory has failed due to the toxicity of the cyanide release on the whole body. [7] It has also been said that laetrile, a semi-synthetic form of amygdalin, is a successful cancer treatment[8].

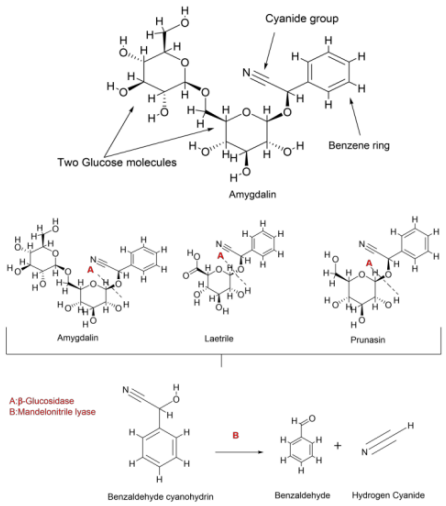

Figure 1. Extracted structure of Amygdalin[8].

The metabolizing enzymes rhodanese (RHD) and β-Glucosidase (BGD) control the

anticancer action. Some studies have found that RHD (which detoxifies cyanide by converting it to thiocyanate) and BGD (which hydrolyzes various glycosides and oligosaccharides) play an essential role in boosting the antigrowth of PC3 cancer cells. This gave insight into a potential route of action for amygdalin. by the mechanism outlined in Figure 2. Malignant cells do not detoxify cyanide produced from amygdalin inside the cell, and the result is the release of free cyanide, which will affect only those cells that contain the enzyme β-Glucosidase[9,10]. This provides amygdalin with reasonable selective toxicity, affecting only the cancer cells that caused it to release the cyanide

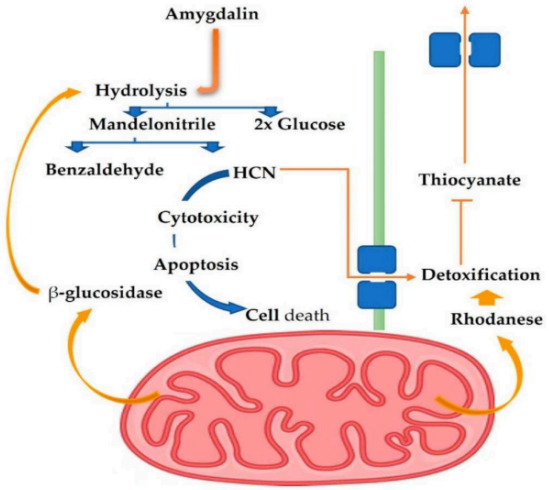

Figure 2 Mechanism of action of Amygdalin/Laetrile. [11]

Most of the background work on amygdalin has been carried out by Krebs and his colleagues[11]. They indicate that cancer is merely a deficiency disease comparable to scurvy or pellagra [12]. Adeficiency of an essential food factor in the modern-day diet initiates the disease[12]. In the case of scurvy, it is a vitamin C deficiency[12]. For pellagra, it is a deficiency of niacin or tryptophan. Various conditions may establish amygdalin deficiency in cancer initiation, such as chemical or dietary factors[12]. Once the deficiency has been established, the cancer will develop at some point in the lifetime with a solid or weak genotype as influenced by the genetic characteristics, phenotype, and surrounding factors[13].

Importance of Investigating Amygdalin as an Anti-Cancer Agent

The discovery of potential anti-cancer properties in amygdalin, also known as amygdalin, has sparked significant interest in the scientific community[2]. This naturally occurring compound has been debated due to its reputation as a potential cancer-fighting agent[3]. As cancer continues to be a leading cause of mortality worldwide, there is a pressing need to explore alternative and complementary treatments. Understanding the mechanisms of action behind the purported anti-cancer effects of amygdalin is crucial in order to assess its potential as a viable therapy, as shown in Table 1.This research aims to critically evaluate existing literature, clinical trials, and experiments to determine the efficacy and safety of amygdalin in cancer treatment[14]. By shedding light on the importance of investigating amygdalin as an anti-cancer agent, this study aims to contribute to the growing body of knowledge on alternative cancer therapies.

Table 1. Amygdalin anti-tumor mechanisms[14].

Type	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.	15
Bladder cancer	Human cells; 10 mg/mL (UMUC-3, TCCSUP or RT112 bladder cancer cells)	17 hours or 2 weeks	Proliferation, adhesion, invasion, migration, cell cycle, cytotoxicity	16
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	17
Prostate cancer	LNCaP (castration-sensitive), DU-145, and PC3 cells (castration-resistant); 0.1 mg/mL, 1 mg/mL, and 10 mg/mL	24 hours or 2 weeks	Proliferation, apoptosis, cell cycle Amygdalin dose-dependently diminished tumor cell growth with maximum effects at 10 mg/mL	18
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.	19
Promyelocytic Leukemia	C57BL/6 mice and AKR mice with BW5147 lymphatic leukemia; 5000 mg/kg	48 hours	Amygdalin induced apoptosis of Hs578T BC cells. Amygdalin downregulated B-cell lymphoma 2 (Bcl- 2), upregulated Bcl-2-associated X protein (Bax),	20
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.	21
Colon cancer	Rat model of colon cancer; 5 mg/mL	24 hours	Proliferation, cell cycle, cytotoxicity Proliferation, apoptosis	22

Understanding Amygdalin and Its Properties

Understanding amygdalin and its properties is crucial in investigating its potential as an

anti-cancer agent. amygdalin, or amygdalin, is a naturally occurring compound in various seeds, nuts, and stone fruits[23]. It has garnered significant interest due to its proposed anti-cancer effects, particularly in alternative medicine circles. Research suggests that amygdalin may exert anti-cancer activity through its metabolite, cyanide, which targets tumor cells selectively. Moreover, amygdalin has been reported to induce apoptosis in cancer cells and inhibit angiogenesis, thereby hindering tumor growth and progression, as shown in Figure 3. However, the safety and efficacy of amygdalin in cancer treatment remain controversial, requiring further rigorous scientific investigation to determine its true potential as a viable anti-cancer therapy[24].By delving deeper into the properties and mechanisms of amygdalin, we can gain valuable insights into its therapeutic possibilities for cancer management[25].

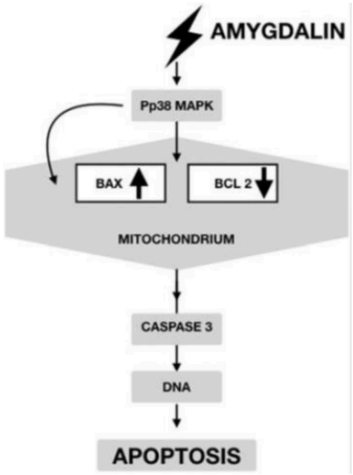

Figure 3. A diagram illustrating the process of apoptosis induced by amygdalin activity; amygdalin activates, which leads to an increase of the level of BAX apoptotic proteins and a decrease of the level of BCL2 anti-apoptotic proteins, and caspase-3 activation, which results in apoptosis[25]. Where:
- RHD: Rhodanese, an enzyme detoxifying cyanide by converting it to thiocyanate.
- PC3: A human prostate cancer cell line used in cancer research to study treatment interactions and responses.
- BAX apoptotic: BAX (Bcl-2-associated X protein) is a pro-apoptotic protein that promotes apoptosis by facilitating cytochrome c release from mitochondria.
BCL2 anti-apoptotic: BCL2 (B-cell lymphoma 2) is an anti-apoptotic protein that helps prevent apoptosis and promote cell survival by inhibiting apoptotic mechanisms.

Evidence Supporting Amygdalin as an Anti-Cancer Agent

Evidence supporting amygdalin as an anti-cancer agent is a topic of significant interest in current medical research. Studies have shown that amygdalin, also known as amygdalin, has potential anti-cancer properties due to its ability to release cyanide selectively in cancer cells,

leading to their destruction while sparing normal cells[26]. Additionally, research indicates that amygdalin may enhance the body's immune response against cancer cells and inhibit tumor growth. These findings highlight the importance of further investigating amygdalin' s therapeutic potential in cancer treatment. It is essential to explore the mechanisms underlying its anti-cancer effects, possible synergistic interactions with conventional treatments, and potential side effects or limitations to its use in clinical practice. By delving into these aspects, we can better understand amygdalin's role as an anti-cancer agent and its potential implications for cancer therapy[26].

Criticisms and Controversies Surrounding Amygdalin

Criticisms and controversies surrounding amygdalin have been prevalent in the scientific community. One major issue is the lack of concrete evidence supporting its efficacy as an anti-cancer agent. Critics argue that the alleged benefits of amygdalin, such as its ability to prevent or treat cancer, have not been scientifically proven through rigorous clinical trials. Additionally, another point of contention is the toxicity of amygdalin, specifically its metabolite cyanide, which can be harmful when ingested in large quantities. Furthermore, marketing amygdalin supplements as a cancer cure without sufficient scientific backing has raised ethical concerns among healthcare professionals, as shown in Figure 4. [27] Addressing these criticisms and controversies is crucial for a comprehensive evaluation of the potential role of amygdalin in cancer treatment[27].

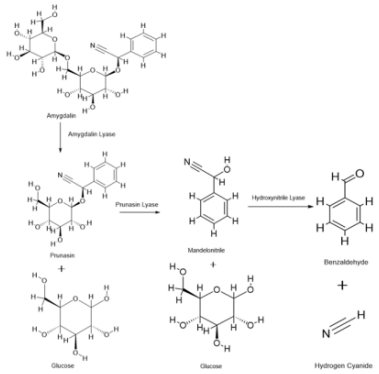

Figure 1. The reaction of amygdalin and the release of cyanide[28].

Therapeutic Potential and Risks of Amygdalin

The therapeutic potential of amygdalin, a cyanogenic glycoside, has been extensively studied through preclinical and clinical research[29]. While laboratory studies indicate some cytotoxic

effects against cancer cells, clinical trials have largely failed to demonstrate significant benefits, raising concerns about its safety due to cyanide toxicity. The following sections outline the key findings regarding amygdalin's therapeutic potential and associated risks[29].

Preclinical Data

Cytotoxic Effects: In vitro studies show that amygdalin exhibits anti-proliferative effects on various cancer cell lines, including human monocytic leukaemia, with mechanisms involving apoptosis and oxidative stress modulation[30]. Research in rats indicates that amygdalin releases significant amounts of cyanide, suggesting potential chronic toxicity in humans[31]. This cyanide release has been linked to potential toxic effects, including chronic toxicity, which raises concerns about its safety for human use. In humans, oral amygdalin intake has significantly increased blood cyanide levels, particularly when metabolized by gut microbes. This underscores the importance of careful dose control and route of administration to mitigate toxic risks[32].

Clinical Trial Results

A clinical trial involving 178 cancer patients found no substantial benefits from amygdalin treatment, with many experiencing symptoms of cyanide toxicity[33].However, cases of severe cyanide poisoning have been documented, particularly when amygdalin is combined with vitamin C, which enhances cyanide release[34].

Current Research and Future Directions

Current research on amygdalin as an anti-cancer agent has focused on its potential cytotoxic effects on cancer cells[35]. Studies have demonstrated that amygdalin, a compound found in amygdalin, could induce apoptosis in cancer cells, inhibit tumor growth, and suppress angiogenesis. Furthermore, research suggests that amygdalin may enhance the efficacy of conventional chemotherapeutic agents, potentially reducing their toxic side effects. While more clinical studies are needed to validate its effectiveness and safety in cancer treatment, the findings thus far suggest that amygdalin has the potential to revolutionize cancer therapy, as shown in Figure 5. Further exploration to fully elucidate the mechanisms underlying amygdalin's anti-cancer properties[32]. Future research directions should include investigating the optimal dosage and administration of amygdalin, exploring its synergistic effects with other anti-cancer agents, and conducting clinical trials to evaluate its safety and efficacy in cancer patients. By addressing these gaps in knowledge, we can better understand amygdalin's therapeutic potential in cancer treatment[29,35].One promising direction is the encapsulation of amygdalin within alginate-chitosan nanoparticles. This approach improves the compound’s stability and enhances targeted release, specifically reaching cancerous tissues while reducing harmful cyanide exposure to healthy cells. Encapsulation in

nanocarriers can extend the release duration, making the therapy more controlled and potentially safer [35]. For instance, alginate-based nano-systems have shown high efficacy for various cancer therapies due to their biocompatibility, sustained drug release, and increased bioavailability. In this way, targeted delivery systems reduce systemic toxicity, a significant limitation for amygdalin, and could overcome the compound's poor pharmacokinetic profile[36].

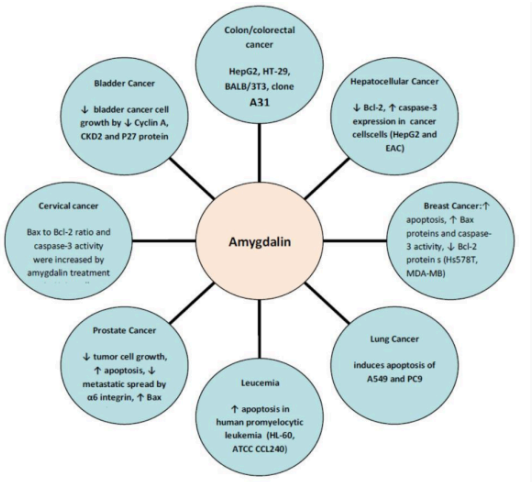

Figure 5. Anticancer molecular mechanisms of amygdalin.

Conclusion

In conclusion, the research on the potential of amygdalin as an anti-cancer agent presents a multifaceted and promising avenue for further exploration and development. A thorough review of the existing literature shows that amygdalin holds a reasonable promise in inhibiting cancer cell growth and inducing apoptosis, potentially offering a natural treatment option for various types of cancer. Furthermore, the range of mechanisms through which amygdalin may exert its anti-cancer effects underscores the complexity of its bioactivity and warrants continued investigation. As such, further research into the mechanisms of action, optimal dosages, and potential synergistic effects with existing treatments is warranted to fully harness the therapeutic potential of amygdalin in the fight against cancer.

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