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Review Article

Review: Amygdalin Loaded Nanoparticles in Cancer Treatment

Mahek Mahebub Shaikh[1], Ajit Pawar[2], Dr. Megha Salve[3]

Department of Pharmacy, Shivajirao Pawar College of Pharmacy, Pachegaon, Tal – Newasa, Dist – Ahmednagar 413725

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ABSTRACT

In 2020, there were about 10 million fatalities and 19 million new instances of cancer, the leading cause of mortality worldwide. According to estimates, the number of cancer cases would rise to nearly 28 million by 2040 due to aging and population expansion[1].Amygdalin has been found to have a number of medical applications, including the treatment of asthma, enhancing immunological function, causing human kidney fibroblasts to undergo apoptosis, and preventing hyperglycemia. To precisely define this herb's function in medical applications, further thorough in vitro and review research is needed.One well-known chemical compound that comes from a variety of fruits is amygdalin. Historically, the glycosides found in this plant have been used as an anticancer drug. An overview of amygdalin's onco-immunity and other therapeutic medicinal uses was provided in this paper. [2]In addition to causing apoptosis, amygdalin has anticancer effects. According to experimental research, amygdalin in cancer cells activates caspase-3 and BAX and inhibits Bcl-2 and Poly (ADP-ribose) polymerase-1 (PARP-1), although there is little information on how these actions work.[3] Pharmaceutical nanocarriers that are currently in use, including liposomes, micelles, nanoemulsions, polymeric nanoparticles, and many more, exhibit a wide range of beneficial qualities, including the ability to treat a number of illnesses, including cancer, diabetes mellitus, metabolic disorders, and genetic disorders. Neurodegenerative illnesses, etc.According to other research, amygdalin has additional pharmacological effects, such as preventing pulmonary fibrosis, inhibiting renal interstitial fibrosis, suppressing and regulating the immune system, resistant to lung injury caused by hyperoxia, and having anti-inflammatory, antitumor, and anti-ulcer properties (Chang et al.[4].

INTRODUCTION

There have been several attempts to create innovative tumor-specific chemotherapy delivery

***Corresponding Author:** Mahek Mahebub Shaikh
Address: *Department of Pharmacy, Shivajirao Pawar College Of Pharmacy, Pachegaon, Tal – Newasa, Dist – Ahmednagar 413725*
Email ✉: mahekshaikh17@gmail.com
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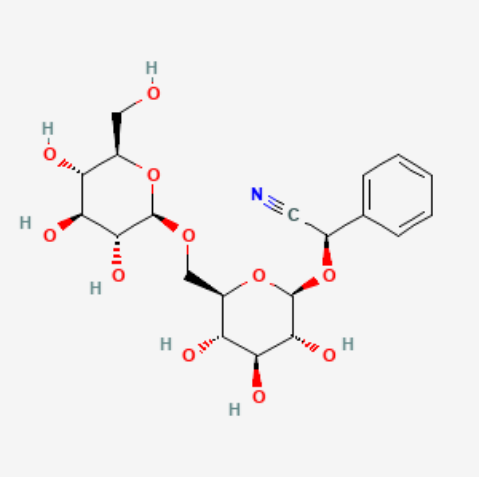
methods to lessen The toxicity and current advancements in nanomedicine have facilitated the creation of more effective and tumor-targeted dose formulations. The US Food and Drug Administration (FDA) and European Medicines Agencies (EMA) have so far approved a variety of nanomedicines, including antibody-drug conjugates (ADCs), drug conjugates, and nanocarriers for cancer therapy. [5] Over the past ten years, both in pharmaceutical research and in clinical settings, the use of nanoparticulate pharmaceutical carriers to improve the in vivo efficiency of numerous medications has been well-established. For pharmaceutical nanocarriers including liposomes, micelles, nanocapsules, polymeric nanoparticles, solid lipid particles, niosomes, and others, surface modification is typically utilized to control their biological properties in a desired way and make them perform.[6] By controlling secretory activity, cell viability, steroidogenesis, proliferation, and apoptosis through extracellular and intracellular signaling pathways, amygdalin affects physiological processes, including female reproduction, at many regulatory levels. On the other side, amygdalin releases large levels of cyanide during its metabolism, which could provide an immediate health risk to people who are susceptible.[7] The main active medicinal component of almonds is amygdalin, which is also frequently present in Rosaceae seeds .In eastern medicine, amygdaline, which was first discovered in rosaceous plants ., including Prunus armeniaca L. var. ansu Maxim, Prunus sibirica L., Prunus mandshurica (Maxim) Koehne, and P. armeniaca L., has been used extensively to treat malignancies, aplastic anemia, and asthma[8]. It is a naturally produced material that is found in the seeds of numerous plant species.[9] should be mentioned that Rosaceae nuclei are the source of the naturally occurring compound amygdalin (D-man-delonitrile-b-D-glucoside-6-b-glucoside). This cyanogenic glycoside is present in a number of fruits .[2] The main focus of current drug discovery research is the use of natural products as a source for novel medications. The seeds of numerous plants in the Prunus Rosacea family, including apricots, apples, bitter almonds, black cherries, plums, and peaches, contain amygdalin, a naturally occurring vitamin B17. This natural substance has drawn a lot of interest.[10]Amygdalin's many medical uses, such as preventing or treating cancer, lowering fever, reducing coughing, and slake thirst, have led to its use as a traditional medication. According to reports from the late 1970s and early 1980s, amygdalin can successfully reduce pain in cancer patients and destroy cancer cells at the tumor site with no systemic effects. But because of the lack of clinical proof of its effectiveness and possible harm, the Food and Drug Administration (FDA) has not authorized amygdalin as a cancer treatment.[11] It is composed of two glucose molecules, one benzaldehyde molecule, and one hydrocyanic acid molecule. Because of its cyanogenic group, which makes it an effective substitute for conventional cancer treatments, amygdalin has been used extensively as a natural anticancer drug [2]. The cancer cell has beta-glucosidases, which are enzymes that produce the deadly chemicals hydrogen cyanide (HCN) and benzaldehyde from amygdalin. The cyanide ion breaks down cancerous cells by obstructing the oxygen that these cells need to function and preventing tumor cells from getting nutrients.[12] When amygdalase and prunase, two glucose-sidase enzymes, hydrolyze it, it can produce prunasin and mandelonitrile before breaking down into benzaldehyde and hydrocyanic acid (HCN). Amygdalin is not hazardous in and of itself, but the HCN it is produced from, which is broken down by certain enzymes, is toxic. [13] Both oral and intravenous (i.v.) administration of amygdalin are possible. In the gastrointestinal system, β-

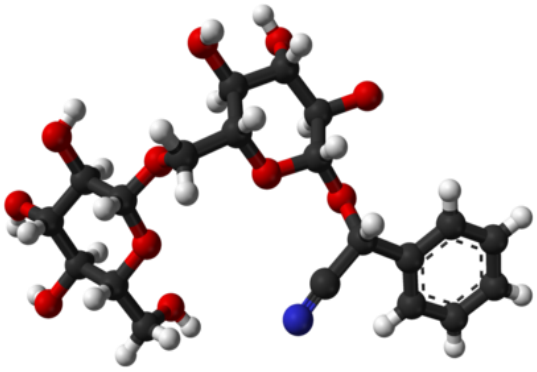
glucosidase-driven cleavage of the terminal glucose residue converts oral amygdalin to D-mandelonitrile β-D-glucoside (prunasin).Bypassing enzymatic breakdown in the gastrointestinal system, intravenous injection of amygdalin is believed to prevent amygdalin-associated cyanide poisoning. [14] Two investigations are reported by Milazzo et al.; one uses intravenous (IV) administration of laetrile, while the other applies laetrile to tumor locations. Both demonstrate a higher survival rate in cancer patients, but they do not fully exhibit a good response . Both patients showed no signs of HCN poisoning, indicating that it is most common when taken orally . After IV and subcutaneous administration, urine contains about 80% thiocyanate (after detoxification by the Rhodanese enzyme) and trace levels of the parent medication .[15] The most popular medical treatments for cancer include surgery, radiation, chemotherapy, and a combination of techniques that are frequently applied in tandem to produce a synergistic effect. Acupuncture, hypnosis, bioenergotherapy, altered diets, and the use of natural compounds such amygdalin are the most popular alternative methods.[16].Numerous targeted treatment approaches, including nanoformulation, have been created to strengthen amygdalin's anti-cancer effects and shield healthy cells from hydrogen cyanide . A water-soluble derivative of chitosan, carboxymethyl chitosan (CMC) has the qualities of gel formation, water solubility, low toxicity, and excellent biocompatibility, making it a viable drug delivery method.[12]

2. Amygdalin – A potential Anti-cancer Agent.

Structure of Amygdalin –



3D structure of Amygdalin



Molecular formula – $C_{20}H_{27}NO_{11}$
molecular weight – 457.429
Melting point -223-226 °C(lit.)
Solubility –Amygdalin's solubility in water and ethanol is:
•Water: 50 g/L
•Ethanol: 1 g/
Uses:

- Managing asthma;
- enhancing the immune system;
- preventing hyperglycemia;
- treating migraine, hypertension, and chronic inflammation;
- enhancing the digestive and reproductive systems;
- improving cerebral function;
- treating cancer

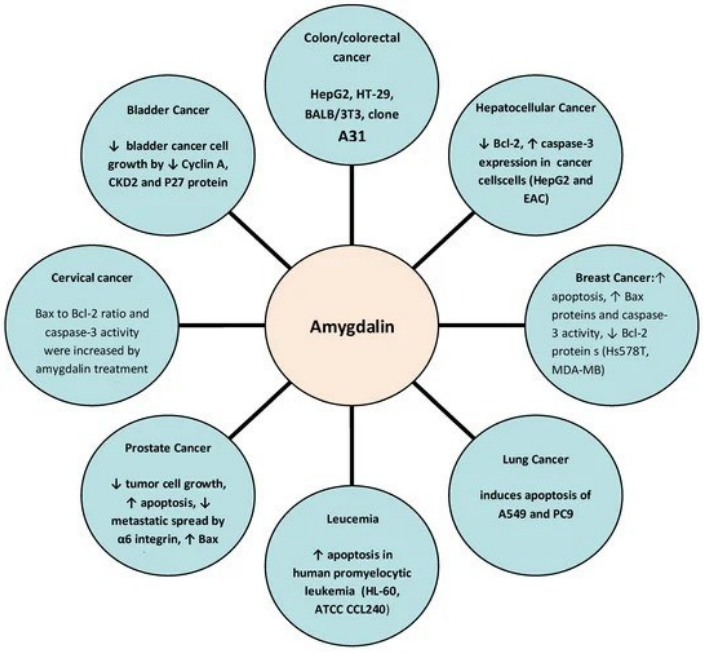


Figure 1: Anticancer molecular mechanisms of amygdalin. ↑: increase, ↓: decrease. [17]

History of amygdalin

The background of amygdalin Robiquet and Boutron-Charlard first extracted amygdalin from bitter almonds (Prunus dulcis) in the 1830s (Wisniak and Robiquet 2013), and Liebig and Wöhler conducted additional research on the subject. Amygdalin was deemed non-toxic based on Widtmann and Denk's self-experimentation and animal testing, which were not fully explained in their article. According to Liebig and Wöhler, pure amygdalin was essential for widespread use (Riecke 1840). In Russia, amygdalin was utilized as an anticancer drug as early as 1845 (Moss 1996). The 1920s saw the earliest accounts of amygdalin use in the US (Curt 1990).[17] In the 1970s, amygdalin was one of the most widely used, unconventional anti-cancer medications; by 1978, 70,000 cancer patients in the US had taken it . However, there has been little and ongoing evidence-based study on amygdalin, and its benefits are debatable. While detractors claim that amygdalin is harmful and ineffectual, supporters view it as a natural cancer treatment. [18].

The National Cancer Institute (NCI) made the decision to assess the effectiveness of amygdalin treatment during this contentious period. The US Food and Drug Administration (FDA) approved a clinical trial that was financed by the NCI, however it did not show anti-cancer activity (Moertel et al. 1982). With a few exceptions, amygdalin has since been prohibited by the FDA and is not permitted for sale as a medication in the USA or Europe (Milazzo et al. 2007). Amygdalin is only permitted to be prescribed under a doctor's supervision in the UK since it is regarded as a "prescription medicine only" (Milazzo et al. 2007).[19] 1873 saw the first isolation of amygdalin. In the US, amygdalin has been taken orally to treat cancer patients since the 1920s. Laetrile, an intravenous version of amygdalin, was created and patented in the 1950s. The names laetrile and amygdalin are used interchangeably despite their chemical differences, which makes it challenging to evaluate clinical data. In this report, "amygdalin" is the only term used.[20] Many studies showed that amygdalin had an antitumor properties (Fukuda et al, 2003) that caused programmed death in prostate cancer (Chang et al, 2006) human cervical carcinoma (Chen et al, 2013) weakened activation of kidney fibroblast

and interstitial fibrosis (Guo, 2013) and blocked bladder cancer cell growth by down-modulating the cell cycle regulating proteins cdk2 and cyclin A (Makareviæ et al, 2014).[21]

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 carci-noma	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 mecha-nism 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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Amygdalin anti-tumour mechanism -

1. Amygdalin treatment in lung cancer –

For a long time, lung cancer has been the most common malignant tumor to cause death globally . Frequently, lung cancer cells spread to the liver, brain, adrenal glands, and other organs.We found that in vitro proliferability of H1299/M and PA/M was decreased, but this inhibition required a higher dose of amygdalin. We observed that using lower amygdalin concentrations for the experiments significantly reduced the in vitro invasive and migratory capacities of H1299/M and PA/M. According to these results, amygdalin was likely to have an anti-metastatic effect on non-small cell lung cancer. This study provides information on the role of amygdalin in lung malignancies that may be useful as a therapeutic target.[22]

2. Amygdalin in colorectal cancer –

Colon cancer is responsible for a significant portion of cancer-related fatalities globally. Typically, immunotherapy, chemotherapy, radiation, surgery, and herbal therapies are used to treat colon cancer. Researchers have focused their attention on nanotechnology as it has been shown to be successful in treating cancer. Table 2 provides an overview of the recent nanoemulsions generated and their uses for colorectal and other cancers, as well as the most common forms of nanoemulsions for various cancer types. Colon cancer accounts for a disproportionate share of cancer-related fatalities globally. The different subtypes of colon cancer are categorized in this section, including cancer that develops on its own, cancer associated with colitis, hereditary

nonpolyposis colon cancer, and familial adenomatous polyposis.[23]

3) Amygdalin treatment in bladder cancer –

With an incidence of 9.6/100,000 for women and 37.9/100,000 for men annually, bladder carcinoma is the second most frequent genitourinary tract cancer in western nations [1]. Transurethral resection, which preserves the bladder, is an option for treating about 70% of first-diagnosed cancers that are superficial. The remaining 30% of tumors have a high chance of metastasizing and develop into muscle invasion Chemotherapy is a treatment option for patients whose disease is locally progressed or metastatic.[20]

4) Amygdalin treatment in prostrate cancer –

Despite recent improvements in the management of metastatic prostate cancer (PCa), resistance will inevitably emerge following taxane therapies, hence there must be efficient ways to counteract drug resistance.The development of resistance following taxane treatments is unavoidable, despite recent advancements in the treatment of metastatic prostate cancer (PCa). This calls for effective alternatives to amygdalin, which dose-dependently inhibited tumor growth and decreased tumor clones in all (parental and resistant) PCa cell lines, along with a G0/G1 phase accumulation. Amygdalin altered cell cycle regulatory proteins considerably. Alongside changes in cytoskeletal proteins and the degree of integrin β1 expression, a mild impact of amygdalin on tumor cell adhesion and chemotaxis was also noted. As a result, amygdalin may inhibit the growth of tumors and the proliferation of taxane-resistant PCa cells. It is need to conduct more research to ascertain amygdalin's. [24]

5) Amygdalin treatment in breast cancer –

Breast cancer is the most prevalent and deadly cancer in women; by 2020, there will likely be 600,000 deaths and 2 million new cases worldwide……..Additionally, it is well known that one of the tumors that is most resistant to chemotherapy is breast cancer cells. It is thought that cancer may continue to proliferate even while traditional illness treatment methods are successful in eliminating cancer cells . Every known chemotherapeutic medication destroys stem cells as well as cancer, and this leads to dangerous side effects. People have been using alternative medicine more frequently to prevent this.[25]

The basic mechanism of Amygdalin as anti-tumour agent-

1) The effect of Amygdalin in apoptosis -

According to 4,6-Diamino-2-phenyl indole (DAPI) staining, HeLa cells treated with amygdalin underwent the normal apoptotic alterations. By double-staining amygdalin-treated HeLa cells with annexin V-FITC and propidium iodide (PI), as well as by increasing their caspase-3 activity, the development of apoptosis in these cells was verified. Additional research revealed that the amygdalin-treated HeLa cells showed an upregulation of the proapoptotic protein Bax and a downregulation of the antiapoptotic protein Bcl-2, suggesting participation in the intrinsic route of apoptosis. By causing apoptosis, amygdalin treatment in vivo suppressed the proliferation of HeLa cell xenografts. Amygdalin may provide a novel treatment option for people with cervical cancer, according to the study's findings .[26]

2) The effect of Amygdalin in cell cycle

The effects of amygdalin on tumor cell proliferation were dose-dependent and peaked at 10 mg/ml. PC3 and LNCaP cells showed decreased apoptosis, but not DU-145 cells, while all cell lines showed lowered colony formation. There was a reported increase in G0/G1-phase cells and a decrease in G2/M- and S-phase cells. Amygdalin was found to alter the cell cycle proteins CDK 1, CDK 2, and CDK 4, as well as cyclins A, B, and D3, after both 24 hours and 2 weeks. Only two weeks later were distinct impacts

on Akt, Rictor, and Raptor activation as well as p19 and p27 expression visible.[27]

3) The cytotoxic effect of Amygdalin –

The glycosidic connection between sugar and aryl groups is hydrolyzed by the enzyme β-glucosidase, which releases glucose. When sugar and aryl groups combine, β-glucosidase inhibits cytochrome c oxidase, the last enzyme in the mitochondrial respiratory chain, which ends the manufacture of adenosine triphosphate and eventually. producing high concentrations of hydrocyanic acid, which results in cell death.12 Tumor cells lack the enzyme rhodanese, which normal cells have to convert hydrocyanic acid to harmless hydrocyanic acid. As a result, hydrocyanic acid can particularly damage tumor cells.13, 14, Li et al.15 discovered that β-glucosidase and amygdalin binding may have a particular anticancer effect. By acting nonspecifically on the cell cycle, hydrocyanic acid can kill cancer cells. The amygdalin can be transformed into an active medication that kills tumor cells precisely when the β-glucosidase is attached to a tumor-specific monoclonal antibody. Todorova et al.16 chose the alkylating chemical methyl methanesulfonate (MMS) as a standard mutagen in order to investigate amygdalin's possible antimutagenic properties. Their research revealed that amygdalin lacked .[28]

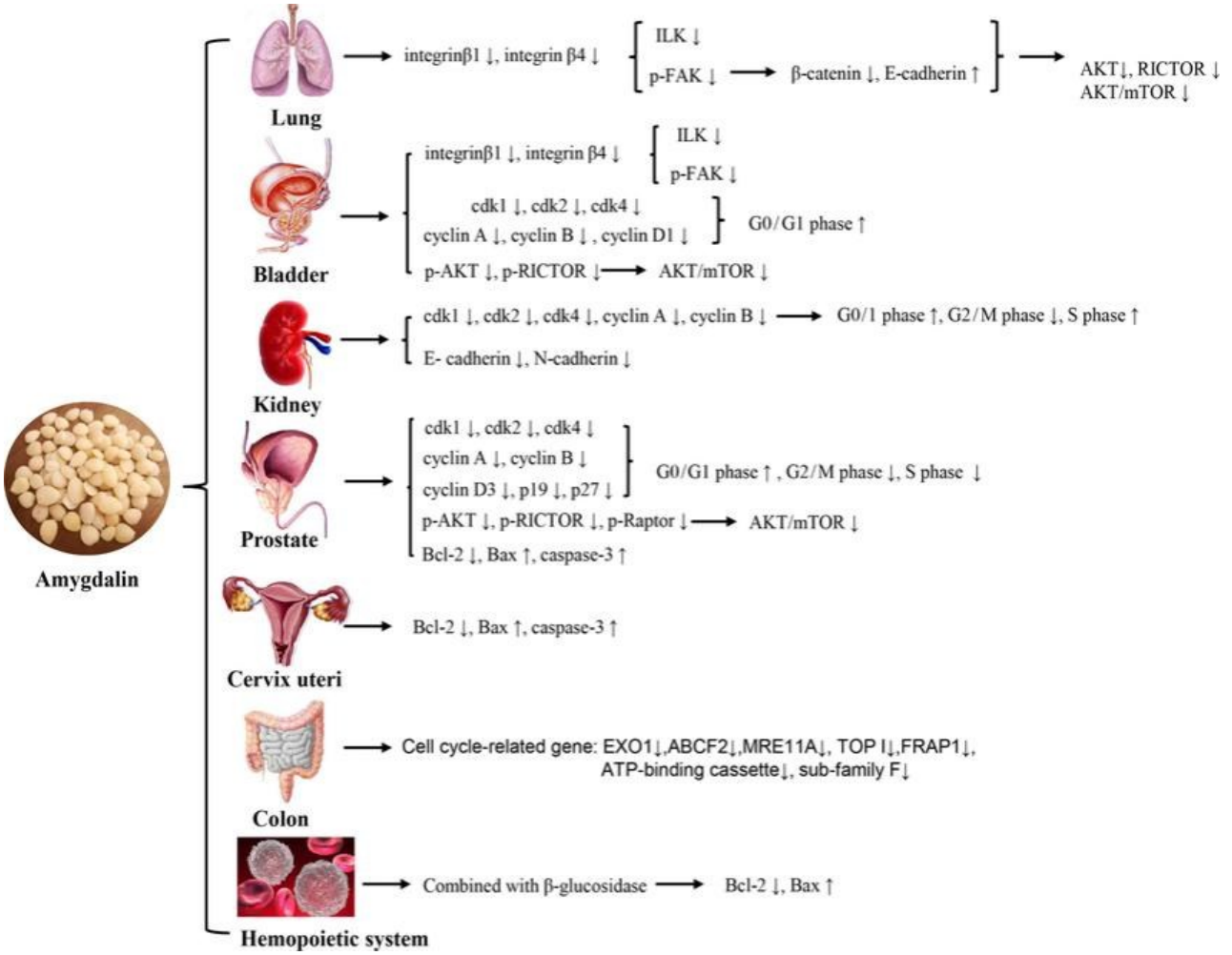


FIGURE 3 : Antitumor effects and mechanisms of Amygdalin. [28]

AMYGDALIN, LAETRILE, AND D-MANDELONITRILE-B-GLUCURONOSIDE CAN BE DIFFERENTIATE:

Laevorotatry mandelonitrile, often known as Laetrile (C14H15NO7), is frequently confused with amygdalin (C20H27NO11). Laetrile is the pure version of amygdalin, which is generally believed to be a substance originating from plants. On the other hand, amygdalin and laetrile have chemical structures (Fig. 1). The confusion between amygdalin and laetrile arose in the 1950s when Kreb and Sons developed an injectable variant of amygdalin and patented it as laetrile (laevorotatory mandeloni-trile) for the treatment of cancer.[18]Laetrile, Amygdalin, and Vitamin B17 are the three interchangeable names. A biochemist by the name of Ernst T. Krebs Jr. isolated vitamin B17 from apricot kernels. In 1952, he also gave it the official vitamin status of Laetrile, which is only short for Laevo-mandelonitrile. However, the systematic investigation of vitamin B17 started when the chemist Bohn (1802) found that hydrocyanic acid was generated when the water from bitter almonds was distilled. In 1830, two chemists from France[29] Laetrile is the active ingredient in medications, and amygdalin is found in related items.[13]

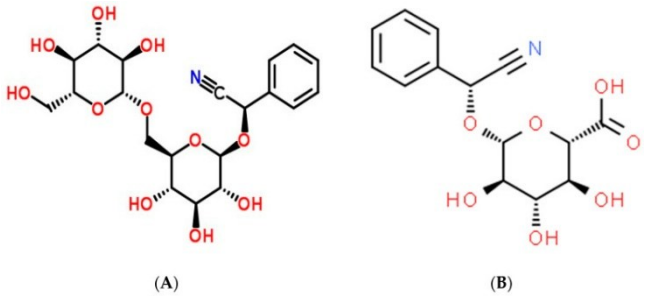


Figure 4: Amygdalin (A) and laetrile (B) chemical structures. [9]

Anydalin toxicity -

Higher blood cyanide levels are also common in those with cyanocobalamin deficiency or hereditary detoxifying deficiencies. The maximum clinical dosage of amygdalin that should be administered is 680 mg/kg [15].Smith and colleagues were the first to report neurological symptoms in patients who consumed amygdalin that were consistent with chronic cyanide poisoning. One of their patients was reported to have prominent neuromuscular abnormalities, such as lower and upper extremities muscle paresis and paral-ysis of both eyes. For seven months, the patient had only been taking one 500 mg amygdalin tablet every day [30].Cyanide poisoning can cause tachycardia, disorientation, nausea, headaches, and, more dangerously, neuromyopathy, cyanosis, coma, convulsions, and death [17]On the basis of this justification, amygdalin has been recommended as a preventative measure to stop cancer. According to our research, oral daily doses of amygdalin will expose people to chronic levels of cyanide, as evidenced by the release of 12.7% of available cyanide in rats after oral administration and 53% of available cyanide after exposure to human fece [30].For other fruits of Poland's climatic zone, data are available. 50 bitter almonds consumed in a short amount of time is thought to be a deadly dose for an adult, whereas 5–10 bitter almonds can be dangerous for a youngster. Amygdalin's fatal dose in adults is thought to be between 0.5 and 3.5 mg/kg body weight Table [16]..Cancer patients should be made aware of the significant danger of experiencing severe side effects from cyanide poisoning from amygdalin or laetrile, particularly if they consume it orally. This risk may rise in vegetarians who are vitamin B12 deficient and in those who consume vitamin C concurrently. [31]

Amygdalin for cancer treatment with nutritional supplements-

Since 1845, amygdalin, laetrile, or vitamin B17 have been proposed as treatments for a number of illnesses, particularly cancers of the tumor [17]Cancer patients should be made aware of the significant danger of experiencing severe side

effects from cyanide poisoning from amygdalin or laetrile, particularly if they consume it orally. This risk may rise in vegetarians who are vitamin B12 deficient and in those who consume vitamin C concurrently [30] However, a number of specialized treatment approaches, including nanoformulation, have been developed recently to strengthen the anti-cancer effects of amygdalin and shield healthy cells from hydrogen cyanide.[32]In addition, some case report studies have revealed that given high dosage of this compound or oral administration can cause cyanide poisoning in patients which results from increased intestinal enzymatic degradation and hydrogen cyanide release compared with the intravenous injection. Therefore, to address these challenges, nano-formulations of amygdalin have been investigated to elevate bio- availability, increase therapeutic efects, reduce the efective dose of amygdalin, enhance the anticancer efects of amyg- dalin and decrease dose dependent side efects [12]Nutraceutical products containing amygdalin are a prospective source for the creation of chemotherapeutic and chemopreventive medications…[33]Amygdalin is a cyanogenic glycoside that is deceptively promoted as a supplement called "Vitamin B17." Go through this article. Exchange the icon Return to the Top Introduction to the Abstract: Mislabeled as a supplement called "Vitamin B17," amygdalin is actually a cyanogenic glycoside. After being eaten, it is hydrolyzed into cyanide in the small intestine, which inhibits cytochrome c oxidase and results in histotoxic hypoxia. Despite being banned by the US Food and Drug Administration, it is being sold online. Following initial successful antidotal therapy, we present a case of significant intentional amygdalin overdose that resulted in recurring cyanide toxicity. Overview of the case: A 33-year-old lady purposefully consumed 20 g of supplements called "apricot POWER B17 Amygdalin." Five hours after intake, her vital signs were as follows: P 127 bpm, BP 112/65 mmHg, RR 25/min, temperature 98.1 °F, and SpO2 98% RA. She was diaphoretic, mydriatic, and in agitated delirium. The VBG she wore.[34]

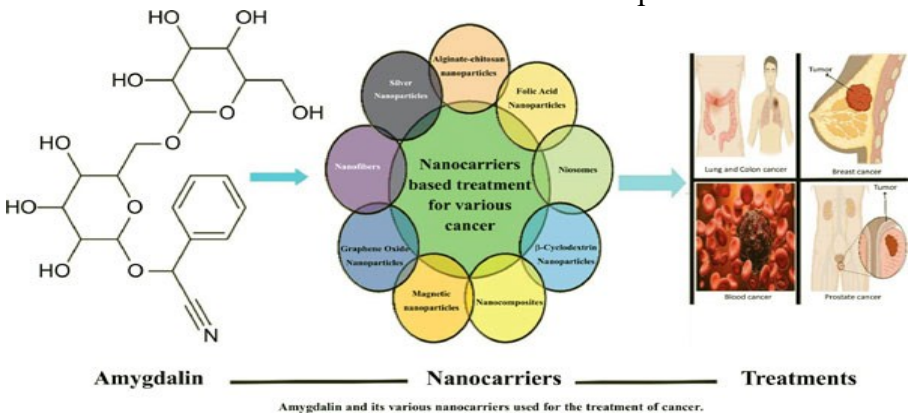
Nanotechnology

Particularly in the area of nano-delivery systems, advances in nanotechnology have found extensive applications in the fields of health and pharmacy. These methods took a long time to guarantee accurate delivery of extremely sensitive molecules, such RNA, to cells at concentrations that produce impressive efficiency, with success rates of 95.0% and 94.5%.[35]Numerous biomaterials with anticancer activity have been created and investigated in vitro and in vivo models in recent years due to the quick development of new technologies like nanoparticles. Rapid drug release and tumor vascular permeability are two of the most important issues with the microsphere and nanoparticle-based methods that were initially proposed to achieve this goal. It is true that different nanoparticles can be combined with suitable therapeutic molecules to improve pharmacokinetic characteristics and increase stability. [36]Opportunities to address and treat difficult diseases have been made possible by the development of medication formulations based on nanoparticles. Although their sizes vary, nanoparticles typically fall between 100 and 500 nm .Drug-related toxicity is reduced by this focused and prolonged drug delivery, and patients are more likely to comply with less frequent doses. Treatments for cancer, AIDS, and numerous other illnesses have benefited from nanotechnology, which has also improved diagnostic testing .[37]High stability, high carrier capacity, the ability to incorporate both hydrophilic and hydrophobic compounds, and the potential for many modes of administration, such as oral application and inhalation, are significant

technological benefits of nanoparticles utilized as drug carriers .[38]

Advantages of nanoparticle drug delivery –

1) Targeted delivery: Drugs can be delivered via nanoparticles to particular tissues or cells, including cancer cells. This can enhance medication effectiveness and lessen adverse effects.
2) Controlled release: It is possible to design nanoparticles to release medications at a regulated pace, which can lessen adverse effects.
3) Improve penetration: Intravenous and other administration methods are made possible by nanoparticles' ability to more readily enter the body due to their small size.
4) Extended shelf life: Nanoparticles are stable and have an extended shelf life.
5) Flexible delivery: Nanoparticles can be swallowed or breathed.
6) Reduced toxicity: Nanotechnology can reduce the toxicity associated with drugs.
7) Better absorption: Drugs can enter tissues, including cancers, more effectively when nanoparticles are present.
8) Decreased premature degradation: Nanoparticles can shield medications from deterioration .
9) Increase Bioavailability:Nanoparticles have the potential to increase the bioavailability of medications.
10) Increased uptake: Drugs with low solubility can be better absorbed when nanoparticles are used.



Amygdalin and its various nanocarriers used for the treatment of cancer.

Figure: Amygdalin & its various nanocarriers use for the treatment of cancer.[49]

Classification of nanomaterials –

A) Based on their dimensionalities, nano-Materials are placed into four diferent classes, summarised in Fig.

The nanomaterials are essential components of nanotechnology. Materials with at least one dimension in the nanoscale, or less than 100 nm, are referred to as nanomaterials…

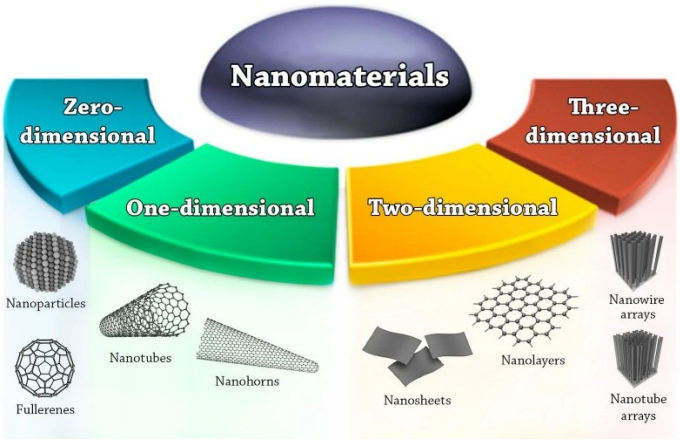


Figure 5: Nanomaterials classifcation based on dimensionality [39]

Nanomaterials classified as

1) zero-dimensional nano material (0-D) have all three dimensions inside the nanoscale range. Nanoparticles, fullerenes, and quantum dots are a few examples.

2) One-dimensional (1-D) nanomaterials: these materials have a single dimension that is not at the nanoscale. Nanotubes, nanofbers, nanorods, nanowires, and nanohorns are a few examples.

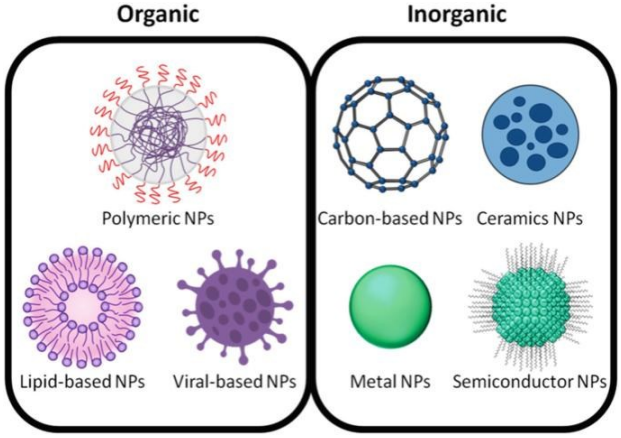
3)two-dimensional nano material (2-D) have two dimensions that extend beyond the nanoscale. Nanosheets, nanofilms, and nanolayers are a few examples.

4)Bulk nanomaterials or tree-dimensional (3-D) nanomaterials are materials that are not limited to the nanoscale in any dimension. Bulk powders, nanoparticle dispersions, arrays of nanowires and nanotubes, etc., are all included in this class.[39]

Classification of nanoparticles (NPs) –

A) Inorganic nanoparticles:
   1) Metal NPs
   2) Ceramic NPs
   3) Semiconductor NPs
   4) Carbon – based NPs

B) Organic nanoparticles:
   5) Lipid based NPs
   6) Polymeric NPs
   7) Viral- based NPs



1) Metal NPs-

Metal nanoparticles are composed entirely of metals. These NPs' well-known localized surface plasmon resonance (LSPR) property gives them unique electrical characteristic.

Types of metal based NPs –

1] Silver nanoparticles (AgNPs)
2]Zinc nanoparticles (ZnONPs)
3] Copper nanoparticles (CuNPs
4]Gold nanoparticles (AuNPs)
5]Aluminum nanoparticles (AlNPs)
6]Iron nanoparticles (FeNPs)

2) Ceramic NPs –

Ceramic nanoparticles (NPs) are minuscule particles composed of non-metallic, inorganic materials that undergo certain cooling and heating processes to impart unique characteristics. They are renowned for their long-lasting qualities and resistance to heat. They can be amorphous, polycrystalline, dense, porous, and hollow.

3) lipid based NPs –

Because these NPs contain lipid moieties, they are useful in a variety of biological applications. Lipid nanoparticles are usually spherical and range in diameter from 10 to 1,000 nm. Lipid nanoparticles, also known as polymeric NPs, are composed of a matrix of soluble lipophilic molecules and a solid lipid core.

4) semiconductor NPs -

Semiconductor nanoparticles share characteristics with both metals and non-metals. Because of this, semiconductor nanoparticles have special chemical and physical characteristics that enable a wide range of uses.

5)Polymeric NPs-

The active ingredients in polymeric nanoparticles (NPs) ranging in size from 1 to 1,000 nm may be confined inside the polymeric body or surface-adsorbed onto the polymeric core. The term polymer nanoparticle (PNP) is frequently used in the literature to describe these NPs, which are frequently organic. [40]

Drug delivery application –

1) Single Drug delivery -

Conjugation with ligands can give liposomes their desired characteristics. Since the conventional mono-branched ligand-modified liposomes typically fall short in delivering a sufficient therapeutic payload, only a small number of liposomes with high targeting efficiency have been developed to date, despite the fact that the mono-targeting ligand can facilitate the binding and internalization of liposomes into the cancer cells [41]When compared to non-targeted nanoparticles, they found that targeted nanoparticles exhibited more cytotoxicity. Additionally, they suggested that endocytosis may be used to encourage the receptor-ligand complex to internalize, increasing the cellular uptake of nanoparticles and potentially facilitating drug administration]. Zhang et al. (2010) also reported a similar outcome in their experiment. According to their outcomes, the overexpression of FRs on HeLa cells may greatly enhance the targeted nanoparticles' uptake by FR-mediated endocytosis, which in turn may lead to increased cytotoxicity [42]FR negative tumor cells (A549) and FR positive tumor cells (KB and HeLa) were used to incubate targeted and nontargeted liposomes. Before FR-targeted liposomes were utilized in cell therapy, free FA was introduced to them as a blocking agent. FCM performed a quantitative analysis of the FR specificity of targeted and nontargeted liposome cellular uptake. At least three iterations of the trials were conducted [43].pH sensitivity and folic acid (FA) targeting into a micelle system to improve medication accumulation in tumor cells and accomplish rapid drug release. Transmission electron microscopy (TEM) and dynamic light scattering were used to characterize folic acid-poly(ethylene glycol)-(+)-α-tocopherol (FA-PEG-VE) and paclitaxel-(+)-α-tocopherol (PTX-VE)-loaded mixed micelles (PHIS/FA/PM) made by poly(ethylene glycol) methyl ether-poly(histidine) (MPEG-PHIS). With an average diameter of 137.0±6.70 nm and a zeta potential of −48.7±4.25 mV, the mixed micelles exhibited a spherical morphology. The loading and drug encapsulation efficiencies were 5.28%±0.30% and 91.06%±2.45%, respectively. Changes in particle size, critical micelle concentration, and transmittance as a function of pH validated the pH sensitivity. According to the MTT experiment, PHIS/FA/PM exhibited reduced cytotoxicity when free FA was present and greater cytotoxicity at pH 6.0 as opposed to pH 7.4. Images from confocal laser scanning microscopy showed cellular uptake that was FA-inhibited and time-dependent. The mixed micelles' targeted accumulation at tumor locations was validated by in vivo imaging, and the tumor inhibition rate was 85.97%. [44] Filomicelles containing folic acid (FA) as the targeted moiety may be a novel strategy. FA receptors (FAR), which are overexpressed in a number of human carcinomas, can be targeted via folate-drug delivery systems, thereby increasing therapeutic efficacy while reducing adverse effects. The purpose of this work was to create filomicelles for the delivery of betulin derivatives by combining poly(L-lactide)-ethylene glycol and poly(L-lactide)-Jeffamine-folic acid [45] .In other body areas, particularly the liver, additional NPs are displaying noticeably stronger signals (Fig. 5B). We anticipated that the biodistribution of NPs with and without folic acid would differ significantly. It's interesting to note that we even noticed a difference between control and orlistat-loaded NPs. When compared to control NPs without orlistat, the tumors treated with folic acid-conjugated orlistat-loaded NPs showed a 70% reduction, according to the data in Fig. 5C. Ten days (Day 14) following the delivery of two doses of NP, the fluorescence signal decreased [46]

2)Dual-drug delivery –

In addition to the straightforward encapsulation of liposomes by a single active ingredient, novel compound formulations are being created.

Combining multiple cytostatic medications in a single chemotherapy cycle is a well-known tactic that depends on combining the various ways that the medications work to potentially provide more potent anticancer effects. Consequently, the co-encapsulation of cisplatin (Cis) and paclitaxel in folic acid-modified liposomes demonstrated that FR-positive non-small lung cancer cells responded more favorably to chemotherapy In cancer cell lines that overexpress folate receptors, FR-targeted liposomes loaded with paclitaxel and imatinib have demonstrated efficacy in accelerating cell death and inhibiting the expression of vascular endothelial growth factor (VEGF) [41] .The results also indicated that FA-PEG-PLGA nanoparticles had no biotoxic effects, the drug delivery system allowed controlled release of the cargo molecules, and the co-delivery of cisplatin and paclitaxel efficiently induces cancer cell apoptosis and cell cycle retardation. In addition, co-delivery of cisplatin and paclitaxel showed the ability to suppress xenograft lung cancer growth and prolong the survival time of xenografted mice. These results implied that FA-PEG-PLGA nanoparticles can function as effective carriers of cisplatin and paclitaxel, and that co-delivery of cisplatin and paclitaxel by FA-PEG-PLGA nanoparticles results in more effective antitumor effects than the combination of free-drugs or single-drug-loaded nanoparticles [47].In order to examine the antitumor effects of co-delivering cisplatin and paclitaxel via a targeted drug delivery system, we employed folic-acid-modified poly(ethylene glycol)-poly(lactic-co-glycolic acid) (FA-PEG-PLGA) to encapsulate the drugs either separately or together. We then assessed the antitumor effects against lung cancer. FA-PEG-PLGA nanoparticles did not cause blood hemolysis, blood coagulation, or complement activation, according to blood compatibility tests and complement activation tests.Additionally, the results showed that the drug delivery system permitted controlled release of the cargo molecules, that FA-PEG-PLGA nanoparticles had no biotoxic effects, and that the co-delivery of paclitaxel and cisplatin effectively induced cell cycle retardation and apoptosis in cancer cells. Furthermore, co-administration of paclitaxel and cisplatin demonstrated the capacity to inhibit the growth of lung cancer in xenograft mice and increase their survival duration. These findings suggested that cisplatin and paclitaxel can be efficiently transported by FA-PEG-PLGA nanoparticles, and that the co-administration of cisplatin and paclitaxel by FA-PEG-PLGA nanoparticles produces more potent antitumor effects than the combination of free drugs or single-drug-loaded nanoparticles.[41]

Future perspectives:

The traditional uses of amygdalini include the treatment of leukoderma, bronchitis, cough, asthma, leprosy, and nausea. Previous in vitro and in vivo research has confirmed its pharmacological effects of anti-tumor, anti-fibrotic, anti-inflammatory, analgesic, immunomodulatory, and anti-atherosclerosis, as well as lowering blood glucose, improving the reproductive and peptic systems, and resolving neurodegeneration and myocardial hypertrophy. Nevertheless, the available research has primarily focused on the pharmacological activity and toxicity of amygdalin, and the molecular processes underlying its activities remain unclear. It is dangerous to employ as a medicinal agent because of the very contentious studies. Analyses of amygdalin's target-organ toxicity and systemic data regarding its pharmacokinetics are both insufficiently understood. Therefore, further investigation is required to evaluate its potential therapeutic effects, adverse effects, or toxicity in the future.Its impact on inflammation, digestion, ineurodegeneration, reproduction, myocardial hypertrophy, and blood glucose has also been the focus of a growing, albeit still incomplete, body of

research in recent years; further research is necessary to fully comprehend this component. Although the current body of research indicates that amygdalin is hazardous when taken orally rather than intravenously, its exact mechanism of action and the dose at which it produces toxicity are still unknown and rely on the gut consortium. In vivo, amygdalin has not been extensively studied or utilized with any drug delivery nanocarriersRecent trials employing amygdalin-loaded ACNPs and an amygdalin/β-Glu-based MDEPT approach may be promising for clinical application in cancer treatments. Thus, more research should be done to examine its encapsulation and anticancer effectiveness in the encapsulated form in order to boost the therapeutic benefit and lessen the negative effects of amygdalin.

CONCLUSION

According to earlier in vitro research, amygdalin inhibited the growth of tumors by influencing the cell cycle, triggering apoptosis and cytotoxicity, and controlling the immune system. Clinical research, however, revealed that hydrocyanic acid can be produced from amygdalin metabolites, and that a buildup of hydrocyanic acid over time could have a harmful and toxic effect on the body. The anticancer capabilities of amygdalin and its synthetic analogue, laetrile, are currently supported by a number of lines of in vitro evidence, and they also seem to be supported by past and planned in vivo animal investigations. But because to their cyano-moiety and low oral bioavailability, there are several serious and urgent problems with their toxicity.

SUMMARY & OVERLOOK

In a number of ways, this study is distinct. Initially, we have incorporated all pertinent published research in the literature. Second, we have listed both in vitro and in vivo experiments to provide a thorough description of amygdalin’s anticancer processes. Lastly, we provide an impartial and thorough summary of the findings of these investigations. The precise anticancer mechanisms of amygdalin in various malignancies are also illustrated with the help of appropriate images and statistics. This evaluation does have certain restrictions, though. First off, there are currently no high-caliber publications on amygdalin, and the experimental and clinical research on the hormone is still in its primary stage. Second, the studies on amygdalin that were retrieved were conducted in various tumor kinds, and not many more investigations were conducted to assess certain molecular pathways. Another area of intense investigation in recent years has been adenosine receptors. They offer a variety of therapeutic benefits, particularly in the management of cancer. Even targeted therapeutic medications have been created and are currently undergoing testing. In order to improve amygdalin's antitumor effect and lessen its side effects for clinical use, more research is needed to clarify the pharmacological mechanisms of the drug, including the ideal dosage, the viability of using it in combination with other anti-tumor medications, and even the artificial synthesis of its active ingredients. A small number of studies on amygdalin's target have been reported.

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