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REVIEW

The Anti-Leukemic Potential of Bee Venom

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Abstract: Bee venom (BV) is a promising candidate against breast and lung, including leukemia. Leukemia is a malignancy related to blood cells that causes abnormal production of leukocytes (WBCs) from bone marrow (BM). Leukemia requires a multimodal treatment approach, including stem cell transplantation, immunotherapy, and chemotherapy. Due to several limitations of current therapies such as drug resistance, severe side effects, high costs, limited targeted treatment options, age-related restrictions, after treatment defects, and the genetic heterogeneity of leukemia, there is a need to explore alternatives such as BV, either as whole or its component(s), or its use in conjugation with other treatments. BV's components such as melittin, found as 40–60% of BV's dry mass, exhibit anti-cancer activity such as pro-apoptotic, anti-proliferative, and cell membrane disruption. BV is a potent inducer of apoptosis, while inhibiting cell survival processes such as the Akt/ERK. BV can be considered as the potent anti-leukemia candidate. Various studies have demonstrated BVs effectiveness on leukemia cell lines such as HL-60, K562, Jurkat cell line, U937 cells, CCRF-CEM, K562, THP-1 cell lines, in a dose-time-cell line-dependent manner. This review aims to comprehend the current research assessing the effectiveness of apitherapy in leukemia through in vitro studies. The limitations of present studies and future possibilities exploring the synergistic effect of BV with the conventional treatments and targeted delivery of BV aimed at enhancing the effectiveness of treating leukemia are also highlighted.

Keywords: bee venom, anti-cancer activity, melittin, apitherapy, dose-time-dependent response, anti-leukemia

Introduction

Leukemia is a type of blood cancer involving abnormal blood cell growth in the bone marrow.[1] Leukemia reduces the hematopoiesis of normal cells due to abnormal proliferation of leukemia cells.[2] There are many risk factors for causing leukemia, which affects people of different age groups, sexes, and geographical locations.[3] Cancer cases are rising faster globally (~12% increase by 2025). In the 2020 Global Cancer Observatory (GLOBOCAN) report, there were about ~19 million cancer cases worldwide.[4] Leukemia ranked 13th worldwide with 2.4% cases, among which Australia (New Zealand) is at the highest rank followed by North America, Europe (Western, Northern, Southern, Eastern), Western Asia and 10th in cancer-related deaths (3.1% fatality).[5,6] In the USA, 1,958,310 new cancer cases were reported in 2023, and the number of leukemia cases was estimated at around 59,610.[7] The total number of leukemia cases in India (2022) is around 55,573 out of 1,461,427, with the number of male patients being 33,604 [Lymphoid (~43%), Myeloid (~46%), others (~10%)] and female patients being 21,969 [Lymphoid (~34%), Myeloid (~53%), others (~11%)].[4] Leukemia has a higher mortality rate and incidence rate, and it is commonly observed in higher-income countries, males, and persons with obesity.[8] Leukemia is classified into myeloid or lymphoid (origin basis) and acute or chronic (progression basis).[1] The standard therapies for treating leukemia are chemotherapy, immunotherapy, stem cell transplantation, targeted therapy and are depicted in Figure 1. Chemotherapy is a treatment that uses chemical drugs (eg, methotrexate[9]) that inhibit tumor progression and promote anti-proliferative activity along with apoptosis directly or indirectly. The chemotherapy can be based on a single drug or multi-drug, but this therapy is toxic due to its negative effect on non-cancerous cells.[10] Targeted therapy is an advancement over chemotherapy, as it specifically targets leukemia cells by blocking abnormalities unique to them, sparing normal cells and inducing leukemia cell death.[11] Immunotherapy by

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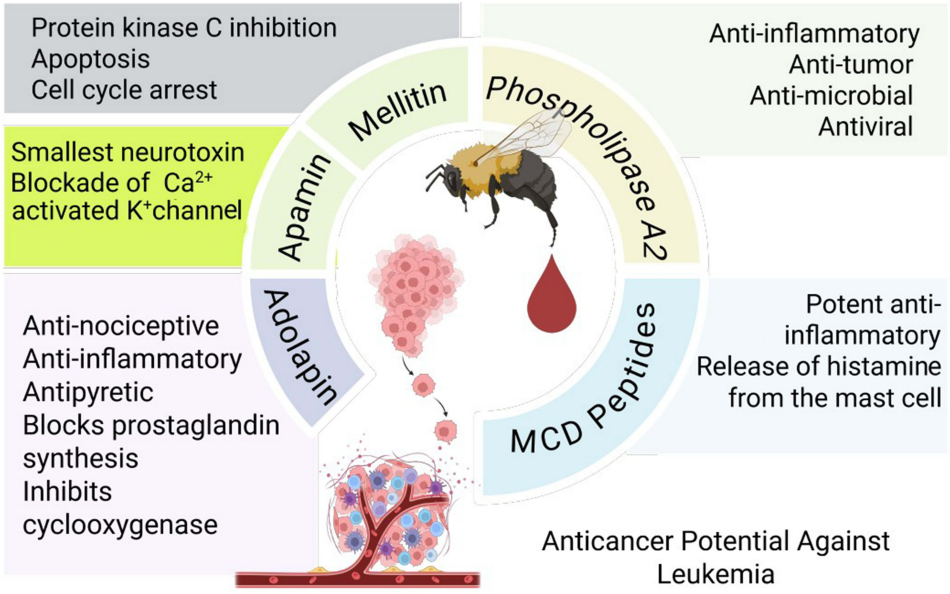
Graphical Abstract



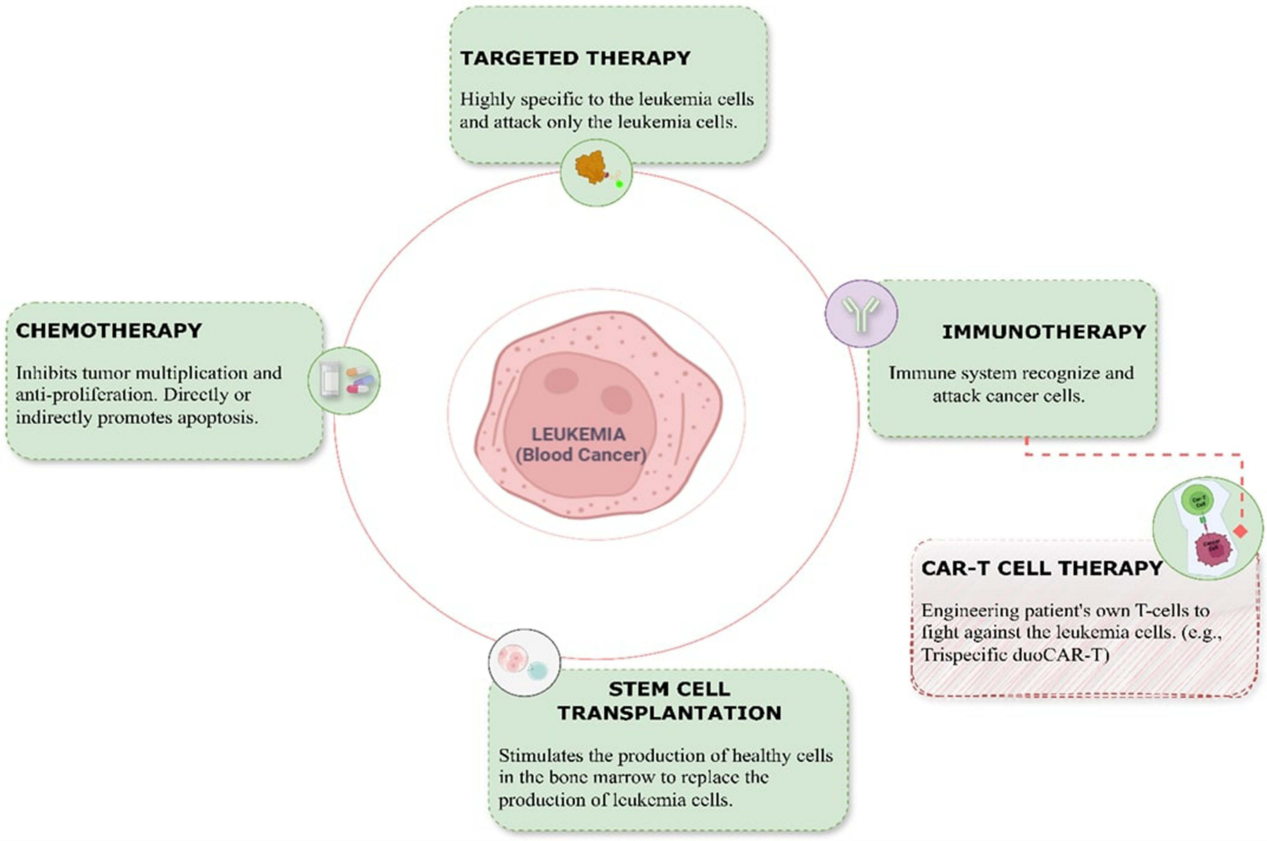


Figure 1 Standard treatment options for leukemia therapy *(Created with draw.io)*.

chimeric antigen receptor-T (CAR-T) cell therapy is a treatment by engineering the immune cells to recognize and act against the leukemia cells.[12] Stem cell transplantation (bone marrow transplantation) replaces leukemia cells with healthy, leukemia-free stem cells.[13]

The aim of the present review is to comprehensively assess the current research scenario studying the anti-cancerous benefits of apothecary in leukemia cell lines, while also addressing the current challenges and futuristic potential of bee venom as a synergistic therapy for leukemia. Possibilities of enhancing its therapeutic potential are also explored.

Recent advancements in clinical studies have led to the use of various therapeutic components derived from natural resources like plants, animals, and insects to tackle various diseases.[14] The survival rate of cancer has increased due to the availability of advanced diagnostic, prognostic, and therapies. One of the new and advanced treatments is BV, which contains anti-cancer component(s) and is used in apitherapy and it has an anti-cancer potential that has been used to treat various types of cancer such as lungs, breast, blood.[15] Sweet BV is a biotoxin used as a pharmacologically active agent by removing its toxic components for pain relief and other disease treatment.[16] BV's primary component, melittin, induces the apoptosis effect by inhibiting the pathological pathways of cancer cells, which support survival.[17] BV is a colorless biotoxin or apitoxin produced from the gland of a bee, and it has many therapeutic properties that help cure skin diseases, neurological diseases, pain relief, etc. and can also be used as an anti-microbial agent.[18] Melittin is the primary component of BV with anti-cancerous properties by creating pores in the phospholipid bilayer, which leads to cell lysis.[18,19] The activation of PLA2 by melittin causes the cell cytotoxic effect, which is the critical mechanism for the anti-cancerous activity of BV.[20] One of the exciting possibilities is combining melittin in conjugate with hormone receptors (eg, Hecate in case of ovarian/testicular tumors), and gene therapy can be used as a novel therapy for cancer treatment.[21] The present review comprehensively explores the potential of BV as an alternative treatment for leukemia. It highlights the possible biomarkers associated with different types of leukemia. It also provides insights into the possibility of integrating other candidates in combination with BV—either in its whole form, its components (such as melittin and phospholipase A2), or analogs of BV (such as synthetic melittin)—on in vitro studies for effective treatment and management of leukemia.

Pathology and Biology of Leukemia

In our daily life activities, there are so many known and unknown factors affecting the health of a person which results in the occurrence of deadly diseases. Leukemia risk factors are classified as smoking, exposure to carcinogens/chemicals (eg, benzene exposure causes AML),[22] past chemotherapy or radiation exposure, blood disorders, age/gender (eg, males are highly affected by leukemia compared to females[23]), family history.[3] Leukemia is classified into several subtypes, including acute or chronic form and lymphoid or myeloid origin.[1] The types of leukemia are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL).[24] Cancer stem cells also play a pivotal role in tumorigenesis and drug resistance.[25] These cells have self-renewal and differentiation properties.[26] Cancer stem cells have unique metabolic flexibility compared to other cells. Leukemia stem cells are responsible for the acute or chronic myeloid leukemia development.[27,28] Tumorigenesis is caused by the dysregulation of pathways that lead to the dedifferentiation of cancer cells, and the expression of specific cancer stem cell (CSC) markers.[25] Leukemia stem cells follow signal pathways (Table 1 [29]), such as activation of Wnt/β-catenin pathway that is responsible for the regulation of cell stemness (BCR–ABL1 oncogene causes CML and incase of FLT-3 mutated AML high level of β-catenin is found).[30] The other pathways involved are Notch, Hedgehog, STAT3, PI3K/Akt/mTOR, Hippo, Ras/MAPK pathways that are critical in cell proliferation.[31–33]

Biomarkers of Leukemia

The biomarkers used for diagnosis and treatment of cancer. Diagnostic biomarkers are used to confirm the type of cancer. In contrast, prognostic biomarkers predict whether the patient has a chance of recovery, survival, or worsening of disease regardless of the treatment.[34] In leukemia patients, white blood cells usually form in bone marrow but do not function properly.[1] Few genetic and protein biomarkers specific to leukemia, as summarized in Table 2.[35–46]

Philadelphia chromosome (Ph) (9;22) (q34; q11) encodes the BCR-ABL1 fusion gene, causes inhibition of differentiation, is anti-apoptotic, pro-proliferative, and supports leukemogenesis. Ph-positive biomarkers can be detected in the

Table 1 Signaling Pathways and Their Role in Leukemia Development

Signalling Pathway	Role in Leukemia Development	Factor/(targets)	Disease	References
Wnt/β- catenin	Dysfunction of destruction complex (Axin, GSK-3β, CK-1α, APC), defects in the expression of Wnt proteins.	LY294002/PI3K/AKT (GSK-3β)	Acute lymphoblastic leukemia (ALL), T-ALL	[29–31]
	Support Leukemia Stem cells [LSC] development.	Activates β- catenin	MLL-LSCs	
	Mutated FLT-3	High level of β-catenin	AML	
Hedgehog	Abnormal activation supports LSCs	Smoothened (Smo), GLI1	AML-LSCs.	[31]
Hippo	Dysfunction of Hippo pathway	Core components (TAP, TAZ, MST1/2 etc.) mutated, YAP/TAZ activates RUNX, SMADS (transcription factors supports leukemia development), Overexpression of LATS2 gene	AML	[32]
		Low expression of LATS2 gene	Acute Lymphocytic leukemia (ALL)	
PI3K/Akt/mTOR	Overactivation enhances the survival of leukemia stem cells.	Forkhead O (FoxO)	CM-LSC	[31]
Ras/MAPK	Overexpression or dysregulation of Ras members	NRas, KRas (mutations)	ALL, AML, CMML, CML	[33]

Abbreviations: GSK-3β, Glycogen synthase kinase-3 beta; CK-1α, Casein kinase 1α; APC, Adenomatous Polyposis Coli; FLT-3, FMS-like tyrosine kinase 3; PI3K, phosphatidylinositol 3-kinase; AKT, Protein Kinase B; GLI1, glioma-associated oncogene homolog 1; RUNX, Runt-related transcription factor; LATS2, Large tumor suppressor kinase 2; KRas, Kirsten – RAS; NRas, Neuroblastoma- RAS.

Table 2 Biomarkers of Leukemia with Their Clinical Relevance

Category	Biomarker	Encodes/Function	Leukemia Subtype	Clinical Relevance	References
Genetic/Molecular	Philadelphia chromosome (Ph) (9;22) (q34; q11)	BCR-ABL1 fusion gene	AML, ALL, CML, MPAL	Diagnostic, targeted by TKI (eg – imatinib, dasatinib)	[35,36]
	PML-RARα (t(15;17))	Nuclear hormone receptor transcription factors	APL (AML subtype)	Diagnostic, Treatment with ATRA-ATO (All-Trans retinoic acid/arsenic trioxide) either alone or in synergy.	[37,38]
	RUNX1:RUNX1T1 oncogenic fusion gene (t (8;21)) (AML1/ETO or MTG8)	RUNX1/RUNX1T1 fusion protein	AML	Favorable prognosis	[39]
	Mutated FLT3	Activates STAT5, MAPK, AKT signalling pathways	AML	Poor prognosis, FLT3 inhibitors	[40]
Protein Markers	CD33	Inhibits pro-inflammatory cytokines (IL-1β/IL-8, TNF-α)	AML	Anti-CD33 drugs/antibodies (Ab) (eg, Gemtuzumab ozogamicin (GO))	[41]
	CD19/CD20/CD22	-	B-ALL	Diagnosis and monitoring by flow cytometric immune-phenotyping and duo-Chimeric Antigen Receptor- T cells (Trispecific duoCAR-T)	[42,43]
	MPO (Myeloperoxidase)	-	APL (AML subtype)	Lineage confirmation, Diagnosis	[44]
	BCL-2	Inhibit apoptosis	CLL, AML	Favorable prognosis, BCL2 inhibitor (eg, venetoclax)	[45,46]

Abbreviations: BCL-2, B-cell leukemia/lymphoma 2; TKI, Tyrosine Kinase Inhibitors.

case of AML, ALL, CML, and MPAL. Targeting BCR-ABL1 by TKI (tyrosine kinase inhibitors) can manage Ph-positive leukemia.[35] The genes responsible for acute promyelocytic leukemia (APL) are two genes that encode for PML on different chromosomes: the PML gene on chromosome 15 and the RARA (retinoic acid receptor α) gene on chromosome 17. The fusion of these two genes produced a fused protein PML-RARα (t(15;17)).[37,38] RUNX1/RUNX1T1 fusion gene, which is the result of chromosomal translocation (8;21) (q22; q22.1) and is found in AML cases (FAB-M2 subtype).[39] Another biomarker is mutated FMS-like tyrosine kinase 3 (FLT3), which "switch-on" signaling pathways (STAT5, MAPK, etc.) that support pro-proliferative activity and inhibit apoptosis and can be detected in AML cases.[40] Another mutated gene, FAT1, is responsible for T-ALL leukemogenesis and can be used as a prognostic biomarker.[47,48] Protein

markers are CD33 (in AML cases),[41] CD19/CD20/CD22 (in B-ALL cases),[43] strong MPO (Myeloperoxidase) expression (in APL cases).[44] The presence of some autoantibodies like VDAC1 (voltage-dependent anion-selective channel 1) and α- enolase may also be used as tools for diagnosis and treatment of pediatric BCP-ALL due to their overexpression in serum of BCP-ALL patients (B-cell progenitor acute lymphoblastic leukemia).[34]

Leukemia and Its Management

Leukemia is a malignant disease that needs frequent monitoring, and the patient needs significant support during treatment. The management of leukemia depends on factors like the stage of disease, subtype, and the patient-specific factor.[49] Current strategies for leukemia include multimodal approaches like chemotherapy, targeted therapy, immunotherapy, hematopoietic stem cell transplantation and combinations.[50] Monoclonal antibody-based immunotherapy is amongst the primary anti-cancer therapies as antibodies directly target the tumor cells and generate anti-tumor immune response.[51] Monoclonal antibodies (mAb) are the proteins that recognize specific antigens. The FDA approves various mAbs for leukemia treatment, like Obinutuzumab (CLL), Ofatumumab (CLL), Inotuzumab ozogamicin (ALL), Moxetumomab pasudotox (Hairy-cell leukemia), Blinatumomab (ALL) and Gemtuzumab ozogamicin (AML), and these antibodies are specific to the antigens they act on and are widely used for clinical treatments.[52] Stem cell transplantation is also one of the new advancements in leukemia cancer treatment, and it is majorly used for curing high-risk acute myeloid leukemia.[53] These therapies have their advantages as well as limitations (Table 3).[52–56] This comparative assessment might be helpful in determining the appropriate therapy/s (sole or in combinations).

The survival rate is higher in younger patients, while older patients (60 yrs above) often show poor outcomes with chemotherapy and allogeneic hematopoietic cell transplantation (HCT).[57] Elderly patients diagnosed with AML (acute myeloid leukemia) have a low survival rate because they are ineligible for intensive chemotherapy treatment, so venetoclax (bioavailable BCl-2 inhibitor) has been used for preclinical studies to induce apoptosis.[58] Based on the results of the national clinical trials (phase 1/2 trials), the response rate is higher. In the Phase 3 trials, venetoclax is accepted as the dose regimen for patients who cannot get intensive chemotherapy.[58] During the initial stage of an encounter with leukemia, through common symptoms like fatigue, fever, abdominal pain, bleeding, and recurrent infections, the patient sees the clinician.[1] After common tests, if leukemia is suspected, then the patient is referred to hematologists or oncologists who do further diagnosis and treatment for leukemia by providing special care and tailored therapy to individual needs. A detailed report is maintained, keeping all records of patient interactions and the changes in patient condition. Proper patient-centered care is done, involving the patient in care decisions and providing clear information and knowledge to the patient.[59]

Table 3 Current Therapies Against Leukemia with Their Advantage and Limitations

Treatment	Advantages	Limitations	References
Chemotherapy	It is a most common and well-established treatment method. This method reduces the leukemia cell count.	It has several side-effects like fatigue, hair loss and immune suppression. Not effective on every patient Resistance develops over a long time	[54]
Immunotherapy	Leads long time remission in the patient's body Optimizes efficacy and reduce risk of toxicity	Not effective for every type of leukemia Risk for immune related effects	[55]
Stem cell transplantation	Potentially curative Reset the immune system with healthy stem cells	Long recovery time High risk of complications	[53]
Monoclonal antibody (mAb)	Can used with combination of different therapies Directly effect on the target tumor cells	Potential infusion reactions Limited for some leukemia	[52]
Targeted therapy	Specifically targets mutation in leukemia Less toxic than other traditional methods like chemotherapy	Only effective for selective genetic mutations Not effective for patients	[56]

Bee Venom: Composition and Significance

Bee Venom Composition

BV or apitoxin (0.1 g dry weight in single drop) is secreted by the honeybees (*Apis mellifera*) is a colourless and odourless compound with an acidic pH of ~5,[18] naturally serves as a defense mechanism against predators.[60] BV contains low molecular weight compounds like sugar, amino acids, and phospholipids, and it has a complex structure containing different components such as apamin, melittin, mast cell degranulating peptide (MCDP), adolapin as well as enzymes like phospholipase2, hyaluronidase (Hya), etc.[14,61] Composition of BV varies based on different parameters such as bee age, season/climate, geographical location, social roles, species, management (nutrition supply)[62] eg, young worker bees such as guards or nurses have high apamin level related to older ones, queen produces high level of histamine and low levels of apamin, melittin and also enzyme levels increase with age.[63] As depicted (Figure 2), the bee venom contains melittin, apamin, adolapin, and hyaluronidase which are mainly response for therapeutic potential against cancer.

Being a toxic compound, it has so many therapeutic properties such as anti-cancer (breast, leukemia etc)., anti-inflammatory (Rheumatoid arthritis; RA), anti-microbial (eg, anti-bacterial effect in case of penicillin-resistant *Staphylococcus aureus*),[64] neurodegenerative diseases treatment (eg, Parkinson, Alzheimer) etc.[15,65] Dominant component of BV, melittin (MF: $C_{131}H_{229}N_{39}O_{31}$; MM: 2846.5 g/mol) is 26-amino-acid residues consists of H-Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-NH_2[66], constitutes 40–60% of the dry BV.[60] Melittin is synthesized from an inactive precursor of 70-amino-acid, "prepromelittin" in a multi-step process.[67] According to the PubChem database (PubChem CID: 16133648), melittin also known as "Forapin" play a role in protein kinase C inhibition, induce apoptosis, cell cycle arrest, anti-neoplastic agent. Melittin disrupts the cell membrane by making pores which lead to leakage of cytoplasm.[68] Apamin, the smallest neurotoxin, accounts for 2%–3% of dry BV that contains 18 amino-acids-residues crosslinked with two disulphide bonds (Cys1–11 and Cys3–15).[69,70] It blocks Ca^2+ activated potassium (K+) channels (SK channel blockade) in neurons (act as allosteric inhibitor) and shows potential in the treatment of fibrosis, central nervous system (CNS) diseases.[70] Mast cell degranulating peptides (MCD) (also known as "peptide 401") accounts for 2–3% of dry BV, consists of 22 amino-acids residues crosslinked with two-disulphide bonds (Cys5-19 and Cys3-15) (similar to apamin)[71] and its biological function is it is a potent anti-inflammatory agent and is responsible for the release of histamine from the mast cell at low concentration.[72] Adolapin (1% of dry BV) consists of 103 amino-acid residues, blocks prostaglandin synthesis and inhibits the cyclooxygenase activity and exhibits anti-nociceptive, anti-inflammatory and antipyretic effects.[15,73] Phospholipase A2 (PLA2) accounts for 12–15% of dry BV and is the most toxic component,[60] consisting of 128 amino-acid residues and four disulphide bonds.[74] It is a calcium-dependent (Ca^{2+}-dependent) enzyme which hydrolyzes the ester bond at sn-2 of

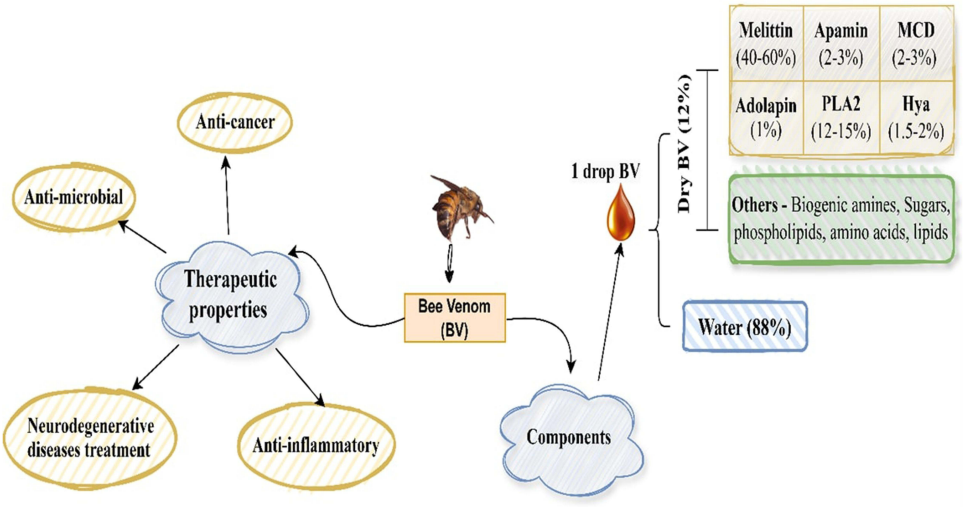


Figure 2 Bee Venom: Components and Therapeutic Properties *(Created with draw.io)*.
Abbreviations: MCD, Mast Cell-Degranulating Peptides; PLA2, Phospholipase A2; Hya, hyaluronidase.

Table 4 BV Components with Their Structure, Mode of Action and Biomedical Properties

Components	Mode of Action	Biomedical Properties	References
Melittin	It induces apoptosis by making pores in the cell membrane	Anti-inflammatory, anti-tumour, anti-microbial	[61]
Apamin	Cross the blood-brain barriers and affect the central nervous system, blocking calcium-activated K^+ channel	Neurotherapeutic effect use for the treatment of neurological disease.	[78]
MCD	Release histamine from the mast cells	Anti-inflammatory and pro-inflammatory agent	[71]
Adolapin	Blocks prostaglandin synthesis and inhibits the cyclo-oxygenase activity	Antipyretic effect, anti-inflammatory, anti-nociceptive	[71]
Phospholipase A2	Cleave the Sn-2 acyl bond, catalytic activity with melittin opening of the melittin-induce channel	Pro-inflammatory enzyme, anti-microbial properties and neurological disorders	[71]
Hyaluronidase	Degrade hyaluronan, increases the blood flow in the area	Enhance the drug delivery, aiding in surgical interventions	[71,79]

phospholipids and generates lysophospholipids (LPLs) and free fatty acids (eg, arachidonic acid (AA) and oleic acid (OA))[75] and exhibits anti-inflammatory, anti-tumor (anti-cancer), anti-microbial, antiviral properties.[15,76] Hyaluronidase (Hya) (Api m2 or spreading factor) composed of 350 amino-acid residues. It helps BV's components to penetrate bloodstream by hydrolyzing the hyaluronic acid.[77] Table 4[61,71,78,79] summarizes different components of bee venom and possible mechanisms involved in biomedical application.

Bee Venom Mechanism of Action

BV has many components, but melittin is the main component with anti-cancerous properties that operate through various mechanisms that treat various cancer cell lines.[80] The mechanism of action includes apoptosis/necrosis, impact on cell signaling pathways responsible for cell survival, membrane disruption and inhibition of cell proliferation (Figure 3).

Apoptosis (programmed cell death) that eliminates damaged cells and maintains cellular homeostasis. One of the anti-leukemia effects of BV's primary component, melittin, is that it induces programmed cell death via an intrinsic pathway by activating pro-apoptotic factors such as Bax or inhibiting anti-apoptotic factors such as bcl-2.[81] Melittin suppresses the activity of bcl-2, the critical protein responsible for cell survival.[82] Melittin affects the mitochondria by damaging its

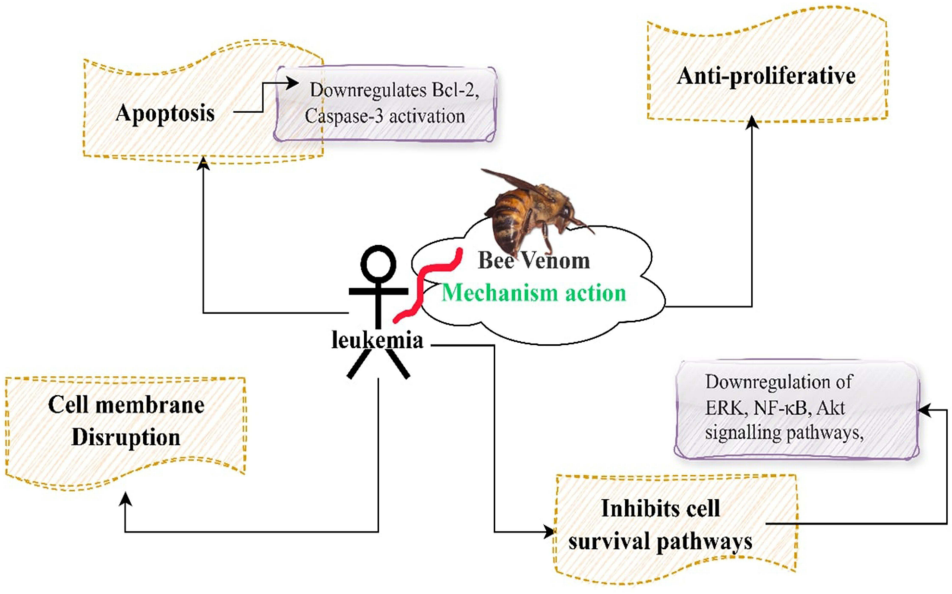


Figure 3 Mechanism action of BV against leukemia *(Created with draw.io)*.

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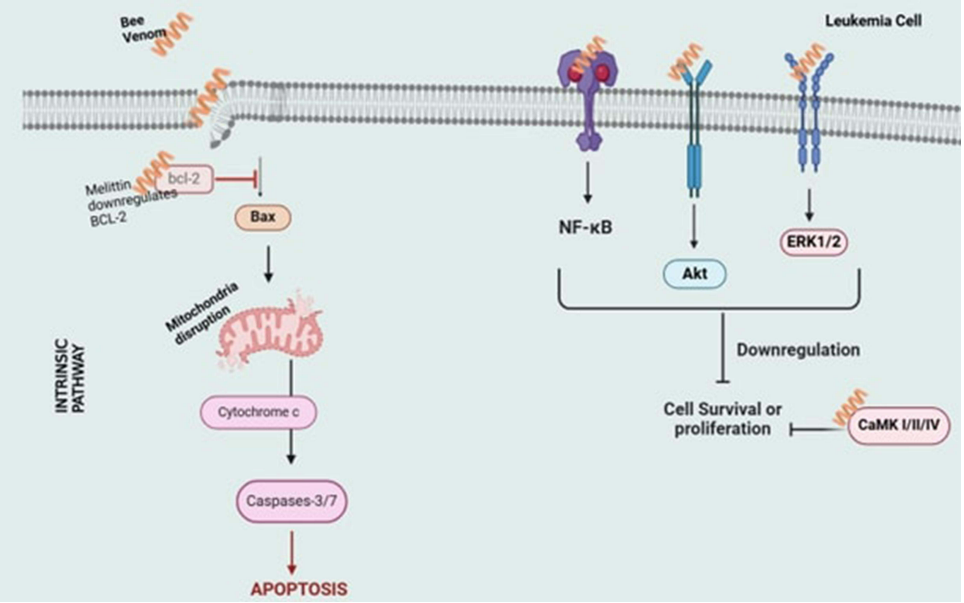

Figure 4 BV disrupts the cell membrane and induces apoptosis (mitochondria-dependent/intrinsic) by inhibiting bcl-2 and activating Bax which activates caspases-3/7. BV also downregulates cell survival processes (NF-κB, Akt, ERK) and also inhibits CaMKI/II/IV which promotes development and the survival of leukemia. *(Created with biorender.com)*.

membrane, affecting the mitochondrial integrity; it also binds to calmodulin (CaM) and inhibits its action, resulting in programmed cell death.[83] Melittin releases cytochrome c and SMAC (the second mitochondrial-derived activator of caspase) from mitochondrial lysis into the cytoplasm, activating the caspases (caspase-3/7).[84] Melittin downregulates the pathways (Akt, ERK etc.) that support self-renewal, cell survival or proliferation of leukemic cells such as causes apoptosis by modulating NF-κβ negatively leads to activation of death receptor.[85] Figure 4 depicts the mechanisms involve in leukemia cells elimination.

Calmodulin (CaM) signaling promotes rapid cell division (proliferation), invasion, and migration, critical factors in tumor formation. The CaMKs play a role in cancer development; for example, CaM-dependent protein Kinases or CaMKs (CaMKI, CaMKII, CaMKIV) can be active in leukemia (myeloid) cases.[86] Melittin binds to calmodulin, inhibits its function, and affects pathways that may support proliferation, survival, etc (eg, P13K/Akt).[83] The role of CaMK in leukemia development and progression has been summarized in Table 5.[86–88]

Bee Venom and Conjugates for Anti-Leukemia Activity

Bee venom or its conjugates are promising candidates for anti-leukemia activity.[89] The effect of Bee Venom depends upon the dose level, time of incubation, and the type of cell line.[17] The mechanisms that induced by the apitoxin for the anti-leukemia activity are the apoptosis, disruption of membrane, cytolysis, necrosis, inhibition of proliferation (anti-proliferative).[89] BV also inhibits the pathway that supports leukemia cell's survival and activates the cell death pathways.[90] As shown in Table 6,[2,61,90–96] the combat property of BV (whole/component) or its conjugates against

Table 5 Role of CaMK in Leukemia Development

CaMK Type	Role in Leukemia
CaMKI (PDB_ID: 1MXE)	Promote leukemia by recruiting SHP-1[87]
CaMKII (PDB_ID: 5VLO)	Proliferation of myeloid leukemia cells (AML), leukemogenesis, CaMKIIg promotes self-renewal of LSCs (inhibit nuclear p27Kip1)[86,88]
CaMKIV (PDB_ID: 2W4O) (UniProtKB: Q16566)	Disrupts the balance between Treg and Th17 cells, inhibits apoptosis and self-renewal of Acute myeloid leukemia[86]

Abbreviation: SHP-1, Src homology region 2 domain-containing phosphatase 1.

Table 6 Effect of BV or BV Conjugates on Leukemia Cell Lines (in vitro Studies)

BV or BV-Conjugates	Cell Line	Dose and Time	Outcome	Other Remark	References
BV + 1,25-(OH)2 VD3 (1,25-dihydroxyvitamin D3as)	HL-60 cells (Human myeloid leukemia cell lines)	5nM of 1,25-(OH)2 VD3 for 72 hours +2.5 μg/mL of BV	Differentiation inductionDownregulation of proliferation	High Conc. à apoptosis Low Conc. anti-proliferative	[91]
Spring time collected - Jordanian crude bee venom (JCBV) extract and MEL	K562 cells (Human erythroleukemic cell line)	JCBV extract IC50 = 3.7 ± 0.3 μg/mL +MEL IC50 = 1.84 ± 0.7 μg/mL	Induces apoptosis, Cell cycle arrest and necrosis	Inhibition of NF-κB/MAPK14 axis expression.	[2]
Synthetic Melittin	U937 cells (human histiocytic lymphoma cell line)	1μM, 10–15 min	Cellular hypertrophy (4–5min) à aggregation (1–2 min) à cytolysis	Membrane permeabilization/pore formation and cell burst (cytolysis)	[92]
Melittin (MEL)	CCRF-CEM (Acute lymphoblastic leukemia cell line)	100 μM, 24hrs 100 μM, 48hrs	92.5% cells undergo apoptosis 95% cells undergo apoptosis	Involved in mitochondrial-dependent cell death pathway.	[61]
	K562 cells (Human erythroleukemic cell line)	100 μM, 24hrs. 100 μM, 48hrs.	93% cells undergo apoptosis 94% cells undergo apoptosis	Involved in mitochondrial-dependent cell death pathway and caspases 3/7 activation, reduces cell viability	
Melectin	K562, K562/ADM, HL-60, THP-1, and Jurkat (Leukemia cell lines)	15 μM 10 μM, 30mins	Inhibit cell proliferation Change in cell membrane	–	[93]
MEL	Jurkat cell line	10−4 M	Out of 100 only 21.5% viable cells.	Reduces bioenergetics of mitochondria which may lead to cell death, Increase cell permeability.	[94]
sTRAIL-melittin	K562	0.5–2 μM	Cytotoxic, Cellular apoptosis		[95]
Sweet bee venom (sBV)	THP-1 (monocytic leukemia cell line)	104 cells were incubated for 48hrs with sBV (10 μg/mL or more dose) sBV (20 μg/mL) sBV (5 μg/mL)/14hr	Inhibit cell growth and apoptosis, necrosis Cell rupture G1 arrest increased	Upregulate Caspase-9 (C9), PARP1, RIPK1/3	[90]
Bee Venom	U937 (human histiocytic lymphoma cell line)	2 or 3 μg/mL for 48 hours	(Decrease cell growth) Inhibits the Bcl-2 and Activate caspase-3 leads to apoptosis	Negatively regulate ERK (inhibited by PD98059) and Akt (inhibited by LY294002)	[96]

leukemia is determined by in vitro studies on the various leukemia cell lines based on the dose level and time of incubation.

HL-60 (Human myeloid leukemia cell lines) on treatment with BV together with 1,25-(OH)2 VD3 (1,25-dihydroxy vitamin D3) enhances reduction in the proliferation of HL-60 cells and increases differentiation into monocytes after 72 hours of incubation at the concentration of 5nM 1,25-OH2 Vitamin D3 and 2.5 μg/mL of BV. However, there was no differentiation when HL-60 was treated only with the BV (2.5 μg/mL).[91] K562 cell line is widely studied using different BV, or it is conjugated such as Springtime collected - Jordanian crude bee venom (JCBV) extract (IC50 = 3.7 ± 0.3 μg/mL),[2] Melittin (100 μM, 24 hrs/48 hrs),[61] Melectin (10–15 μM, 30 mins),[93] sTRAIL-melittin (~2 μM)[95] which inhibits the survival of the cell, causes necrosis, cell death, and reduces NF-κB/MAPK14 axis expression.[2] Sweet Bee Venom (sBV) affects the THP-1 cell lines differently as per the dose and time, such as 10 μg/mL or more dose causes anti-proliferative properties and programmed cell death, at (20 μg/mL), rupturing of cells takes place, and at (5 μg/mL)/14 hr, an increase in G1 arrest.[90]

Future Prospective

Bee venom (BV) or its major component melittin alone or in combination of chemotherapeutic agents induce apoptosis in cancer cells and also show anti-proliferative activity. The synergy of chemotherapeutic agents/natural products with BV stimulates good anti-cancer activity and reduces the dosage of therapeutic agents which simultaneously reduces the side-effects. BV shows cytotoxic effect through the activation of PLA-2 by melittin.[17] There is an evidence that supports that the palladium complex has a synergistic effect with the bee venom in case of leukemia (mainly on the T-cell lymphoblastic leukemia cells or T-ALL cells) by activating the caspase-3 dependent apoptotic pathway.[97] Also, temozolomide drug in combination with the bee venom component (melittin) can lower down the growth and proliferation of the cancer cells.[18] More study is required to find out other and efficient compounds which can be used along with the bee venom in controlling the leukemia. The recent discoveries of enzymes such as acid phosphatase and superoxide dismutase in BV of Egyptian honeybees have further explored the anti-microbial and anti-tumor potency of BV.[98,99] The conventional delivery of bee venom is done through injections, ointments, tablets, lotions and controlled drug delivery system, but these classical methods have some drawbacks like protein degradation through gastrointestinal enzymes, causes sting induced inflammation and no proper delivery of bee venom at affected site.[18] Modern therapeutics have developed the nanoparticles or nano-delivery system which are formed from the biodegradable polymers, the BV is encapsulated in these nanoparticles which provide a sustain release and efficacy to reduce the patient compliance and the administrative intervals.[100] More research is required to deliver the bee venom (BV) or its components to the target site efficiently.

Conclusions

The “chemo-preventive” approach provides a platform for the natural products as a therapeutic agent against the cancer with reduced side-effects and one of them is the BV. The anticancer activity of BV plays a promising role in the treatment of various cancers. Thus, the anticancer potential of BV can be considered as a perspective and prospective way of leukemia therapy. This ability of BV to target only the cancer cells without affecting physiological cells is a potential advantage over the conventional treatments. Thus, as research develops, the use of bee venom therapeutic properties may provide new strategies for the management of leukemia and other cancer types in the clinical practice. The further studies of the action and the effect of BV are not only helping to improve the outcome of the patient but also to enhance the understanding of cancer. However, translating these preclinical findings into clinical applications remains challenging and requires optimizing bioavailability while minimizing systemic toxicity, addressing individual variability in response due to genetic and immunologic factors, and generating robust clinical evidence through well-designed trials to confirm safety and efficacy along with the dose optimization and delivery mechanism. In the future, it is possible that using natural products like bee venom (BV) we will be able to make innovative advances in the treatment of cancer.

Data Sharing Statement

All the data associated with manuscript has been included in the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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