MOLECULAR DOCKING OF VARIOUS ALKALOIDS AGAINST ABL-KINASE FOR ANTI-CHRONIC MYELOID LEUKEMIC PROPERTY

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

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CANDIDATE'S DECLARATION

I, **Pratibha Yadav [2K21/MSCBIO/33],** student of **M.Sc. Biotechnology,** hereby declare that the project Dissertation titled **"Molecular docking of various alkaloids against ABL-kinase for anti-chronic myeloid leukemic property"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirements for the award of the degree of Master of Science, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateships, Fellowship or other similar title or recognition.

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CERTIFICATE

I, hereby certify that the Project Dissertation titled, **"Molecular docking of various alkaloids against ABL-kinase for anti-chronic myeloid leukemic property"** which is submitted by, **Pratibha Yadav [2K21/MSCBIO/33],** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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ABSTRACT

Chronic myeloid leukemia is a bone marrow cancer that results from the reciprocal translocation of chromosomes 9 and 22, which produces the activated tyrosine kinase that results in unchecked cell proliferation and various other signaling cascades that block apoptosis. Tyrosine kinase inhibitors, like nilotinib, effectively slow the course of CML but not in drug resistance. Despite the availability of a variety of Tyrosine Kinase Inhibitors (TKI), treatments are rendered ineffective due to side effects and multi-drug resistance. Alkaloids, flavonoids, terpenoids, lignans, and saponins are examples of natural products with antileukemic properties that are also less toxic and effective against multi-drug resistance, making them an alternative and viable treatment option. NPs not only can combat CML cells' multi-drug resistance (MDR) as well as can separate them into the monocyte/erythroid lineage. In this paper, we will discuss the pathophysiology of chronic myeloid leukemia (CML) and the importance of various alkaloids in treating CML. In molecular docking of various antileukemic alkaloids with ABL-kinase, Curine shows maximum binding affinity using nilotinib as a control depicting its highly effective antileukemic property which can be used to formulate various other novel treatments for CML.

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PRATIBHA YADAV

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LIST OF KEYWORDS AND ABBREVIATIONS

CML: Chronic Myeloid Leukemia

BCR: Breakpoint cluster region

ABL: Abelson murine leukemia

TKI: Tyrosine kinase Inhibitor

TFR: Treatment-free remission

MDR: Multi-drug resistance

BP: Blastic phase

CP: Chronic phase

GRB:Growth factor receptor bound protein

GAB2: GRB associated protein 2

GMP: Granulocyte-macrophage progenitors

PI3K: Phosphatidylinositol 3-kinase

AMPK: AMP-activated Protein Kinase

PMC: Peripheral mononuclear cells

RAS: Rat sarcoma virus

STAT1 Signal Transducer and Activator of Transcription 1

STAT2 Signal Transducer and Activator of Transcription 2

ERK: Extracellular signal-regulated kinases

EGFR: Epidermal growth factor

CHAPTER 1
INTRODUCTION

Chronic myeloid leukemia is myeloproliferative neoplasm caused by the reciprocal translocation of chromosomes 9 and 22 [t (9;22)], this causes the Philadelphia chromosome to develop.. The fusion gene is created as a result of this translocation. BCR-ABL1, an oncogene that produces an oncoprotein with tyrosine kinase activity that causes uncontrolled cell division and resistance to apoptosis. The first description of chronic myeloid leukemia was made in 1845 by John Bennett and Rudolf Virchow, who independently reported a case of splenomegaly and leukocytosis in their journal paper[1][2]. Pete Nowell and Dawid Hungerford discovered a small unusual chromosome in chronic myeloid patients almost a century ago; this chromosome is known as the "Philadelphia chromosome." Abelson murine leukemia oncogene (ABL-1) was found by Nora Heisterkamp and Jim Groffen after a number of discoveries. It is located on chromosome 9 and translocate to chromosome 22 [3].

Multiple symptoms, including splenomegaly, anemia, weight loss, and others, are brought on by chronic myeloid leukemia (CML)[4]. In 2020, 8,450 individuals with a diagnosis of chronic myeloid leukemia passed away, accounting for about 1,130 of those deaths[5].

To treat CML TKI can be used, and TKI used is based on the patient's tolerance and efficacy[6]. Currently, the vast majority of patients have a typical life expectancy. and experience treatment-free remission (TFR) as a result of the development of three generations of TKIs[7]. There are three stages to this illness: the chronic, accelerated, and blast phases. It may progress to an accelerated phase if not treated quickly.

The most popular therapies for each form of leukaemia nowadays include chemotherapy medicines, radiation therapy, and monoclonal hematopoietic stem cell transplantation. The course of therapy depends on the patient's age, the patient's age upon diagnosis, and the subtype of leukaemia. Despite being utilised in clinical settings to treat leukaemia, chemotherapy medications like doxorubicin, fludarabine, prednisone, chlorambucil, and cyclophosphamide are frequently administered in combinations rather than alone and have little effect on a patient's overall survival rate [8]. For ALL people, there is a chance of death from infections, gastrointestinal and liver toxicity, oral mucositis, and cardiac and neurological issues, and significantly decreased bone mineral density in children are

all side effects of intensive chemotherapeutic treatment for leukaemia patients.[8]

The main therapeutic approach for treating leukaemia is still chemotherapy. The existing medications, however, possess a high level of widespread cytotoxicity that is harmful to both healthy and unhealthful cells. Consequently, the search for potential anticancer medicines in medicinal plants has grown over time.

Despite having a number of negative side effects, taking these medications excessively causes leukaemia cells to develop chemotherapeutic treatment resistance. As a result, increasing the average life expectancy depends on the development of new medicinal medications with better efficacy and lower toxicity [8]. There is a long tradition of using medicinal plants to treat a wide range of diseases, including various cancers. Due to their abundance and diversity, plant-based bioactive chemicals are regarded as sustainable sources of anti-leukemic medicines.

The capacity of pure chemicals and crude extracts from plants to replace currently used pharmacological therapies for leukaemia has been questioned in light of research on the anti-proliferative capabilities against leukaemia. TKIs were created to be competitive with the BCR-ABL's ATP binding site. TKIs successfully suppressed wild-type BCR-ABL; however, BCR-ABL mutations and post-treatment upregulation of drug efflux proteins reduced their effectiveness.

Since a different approach to the It's necessary to develop new BCR-ABL inhibitors. NPs (obtained from live organisms) offers a different, efficient, and affordable design for treatment. They also have fewer adverse effect. Numerous NPs suppress CML cell growth and even cause cell death by apoptosis, according to studies done so far. The MDR can be reversed by NPs by itself or when combined with other TKIs, enhancing the responses of TKIs to CML.

In this paper the anti-leukemic capabilities of ethnomedicinal plants are reviewed, discussed, and their possible effectiveness is discussed in this article. Also mentioned are potential ways by which pure chemicals and isolates their harmful effects against leukaemia.

CHAPTER 2
LITERATURE REVIEW

2.1 Pathophysiology of chronic myeloid leukemia:

Philadelphia chromosomes are formed in CML patients by genomic recombination of the ABL gene situated on chromosome 9's long arm and the BCR gene on chromosome 22's long arm [9]. The ABL gene has 11 exons, a tyrosine kinase site, a DNA binding domain that interacts with the nucleus, an acting binding domain that interacts with the cytoskeleton in the cytoplasm. [10].

Tyrosine kinase is negatively regulated by SH3 in the normal ABL gene. The BCR gene has 23 exons and includes the tyrosine 177 domain, the Rho/GEF domain, the oligomerization domain toward the N-terminus, and many other domains[10].

Both the ABL and BCR genes have different breakpoint regions [11]. On the BCR gene, there are three breakpoint regions: a major one between intron 13 and 14; a minor one between intron 1 and 2; and a micro breakpoint point region between exon 19 [4]. Between exons 1 and 2, the ABL gene typically contains a breakpoint region [4]. Fusion of exons 1 and 13 of the BCR major transcript (e13a2) is more frequently observed in patients with CML than with AML. However, CML patients rarely have the minor transcript (e1a2) that forms the 190kDa protein[10]. E19a2 micro-transcript produces 230kDa protein [9].

Chimeric BCR-ABL gene formation occurs after translocation. The oligomerization domain disrupts the negative control of SH3 activity, resulting in active tyrosine kinase, which in further phosphorylates RAS protein and drives the MAPK and pathways like ERK in a constitutive manner, ultimately causing uncontrolled cell division and resistance to apoptosis.

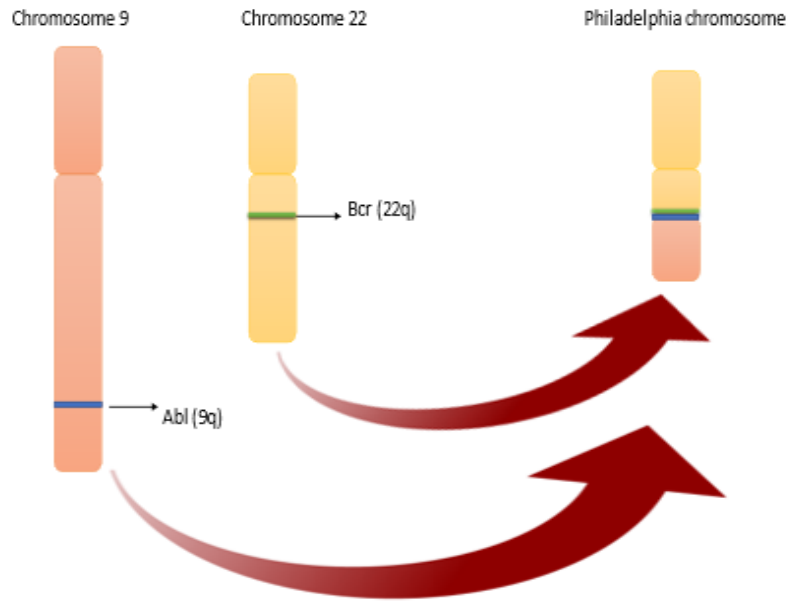


Figure 2.1: Showing translocation between chromosome 9 and chromosome 22 forming Philadelphia chromosome.

2.2 Various signalling occurring in chronic myeloid leukemia

Bcr-abl codes for tyrosine kinase enzyme that further activates various pathways indulge in cell survival and cell division, like the RAS, MAPK, JAK-STAT, and PI3K pathways [12]. Numerous connections between Ras and Bcr-Abl have been identified. Since then, multiple BCR-ABL-positive cell lines have been found to have activation of Stat transcription factors (Stat1 and Stat5), and Stat5 activation seems to play a part in the cancer development. Furthermore, a number of studies revealed that DNA damage does not trigger apoptosis in BCR-ABL-positive cell lines. It is yet unclear what biological processes underlie these processes[13]. The phosphorylation process of the pro-apoptotic protein Bad may also be connected to the suppression of apoptosis by BCR-ABL. Along with Akt, Raf-1 phosphorylates Bad on two serine residues in the region right after Ras[13]. It is usually challenging to distinguish between the proliferative and anti-apoptotic effects of the several signals stimulated by Bcr-Abl . As a result, Bcr-Abl could shift the scales in favour of apoptosis suppression while also stimulating cell proliferation.[13]

The new finding that Bcr-Abl causes the degradations of the inhibitory proteins Abi-1 and Abi-2 by the proteasome may be the first sign of another mechanism through which

Bcr-Abl causes changes in cell. The break down of Abi-1 and Abi-2 is unique to Ph-positive acute leukaemias and is not present in Ph-negative samples with identical phenotypic, which is the most convincing evidence.[13]

Despite the FDA's approval of several first- and second-generation drugs, including Gleevac and Nilotinib, Destanib, and Bosutinib, multidrug resistance (MDR) and bcr-abl gene mutations make these medications less effective. Natural products with anti-CML properties, such as alkaloids, flavonoids, terpenoids, lignans, etc., are an alternative option for treatment with minimal or no side effects.

Some of the processes and routes through which BCR-ABL1 causes the CML phenotype have been elucidated by mutagenesis experiments. Leukemogenesis requires two crucial motifs in the protein's BCR region. One of them is a coiled-coil oligomerization region that promotes cross-phosphorylation, and stimulation of the fusion protein at the protein's extreme N-terminus [14]. The other crucial motif is Tyr177, which is phosphorylated in in leukaemia cells and works as a binding site for the GRB2 adaptor protein. GRB2 then activate the phosphatidylinositol 3-kinase (PI3K) and SHP2 signalling pathways, both of which are involved in leukemia development. According to a latest research, GAB2 signalling shields CML cells against several BCR-ABL1 TKIs.[14]

PI3K/AKT/mTOR pathway:

Several other products of the PI3K/AKT pathway are being demonstrated to take part in Induced leukomogenesis by BCR-ABL1as a result of the PI3K/AKT pathway being activated by BCR-ABL1 with the help of GAB2. BAD phosphorylation results from PI3K/AKT activation and blocks the BCL-2 anti-apoptotic protein from attaching to it and becoming inactive[14]. Contrarily, BCR-ABL1 causes phosphorylation of of FOXO3a transcription factor in myeloid progenitors by activating PI3K and AKT.

A critical function of the mTOR to control mRNA translation. in mammalian cells, which in turn regulates cell growth and proliferation. The mTOR which is serine/threonine kinase works in PI3K/AKT pathway[14]. The catalytic subunit/kinase of the two different protein complexes, called mTORC1 and mTORC2, is mTOR. For BCR-ABL1- modified cells to develop and survive, TORC1 and TORC2 are crucial.

For BCR-ABL1-transformed cells to proliferate and survive, TORC1 and TORC2 are

crucial. In addition to inhibiting TORCs directly, it has also been investigated to limit mTOR activity indirectly through altering the AMP-activated Protein Kinase (AMPK) pathway. The possibility of utilising AMPK activators for the treatment of Ph+ leukaemias resistant to TKIs is increased by the fact that AMPK stimulation results in mTOR inhibition regardless of TKI sensitivity[14].

RAS/RAF/MAP kinase

The SH2-dependent interaction of GRB2 is mediated by tyrosine 177 found in the BCR region of BCR-ABL1. In addition to GAB2, SOS, a guanine nucleotide exchange factor of RAS that promotes RAS activation, is another effector of GRB2. There is strong scientific evidence that BCR-ABL1 triggers the RAS/RAF/MEK/ERK pathway, which in turn activates ERK. In stem cells from embryos converted by BCR-ABL1, the ERK1/2 cascade is actually active, and ERK2 activation could have a role in imatinib resistance[14]. Farnesyltransferase inhibitors work in concert with MEK/ERK inhibitors to limit proliferation and viability in K562 CML cells and in initial chronic phase CD34+ CML cells by inhibiting the RAS pathway.

JAK/STAT pathway

Despite substantial research, the function of JAK kinase in the pathophysiology of CML remains unclear. In BCR-ABL1-expressing cells, JAK kinase including JAK2, are unmistakably active, however JAK2 is not the kinase that activates STAT5. JAK2 kinase inhibitors can reduce the survival and proliferation of BCR-ABL1 positive cells in culture, but JAK2-deficient progenitors are also susceptible to these medications, suggesting that receptors other than JAK2 are the cause. The recurrence of CML LSC did not get ruled out, yet, and JAK2 signalling may be a factor in CML patients' resistance to TKI treatment[14].

WNT/β-catenin

A landmark work that found abnormal constitutive nuclear catenin in granulocyte-macrophage progenitors in individuals with blast crisis was the first to link the WNT/-catenin pathway to CML. Nuclear -catenin was thought to be linked to aberrant regeneration in the tumour GMPs since it is normally only seen in the HSC compartment[14]. Gene expression study that revealed elevated expression of multiple

WNT targets, which include c-MYC, cadherin, ROK13A, MDI1, , during the accelerated and blast further linked WNT in the course of the CML illness. Recent research hypothesised that catenin is necessary is specific to CML stem cells vs. normal HSC, suggesting a viable pharmacologic concentrate in this CML. Further research on a mice retroviral CML model showed that catenin deletion damaged the growth of CML-like MPN triggered by BCR-ABL1[14].

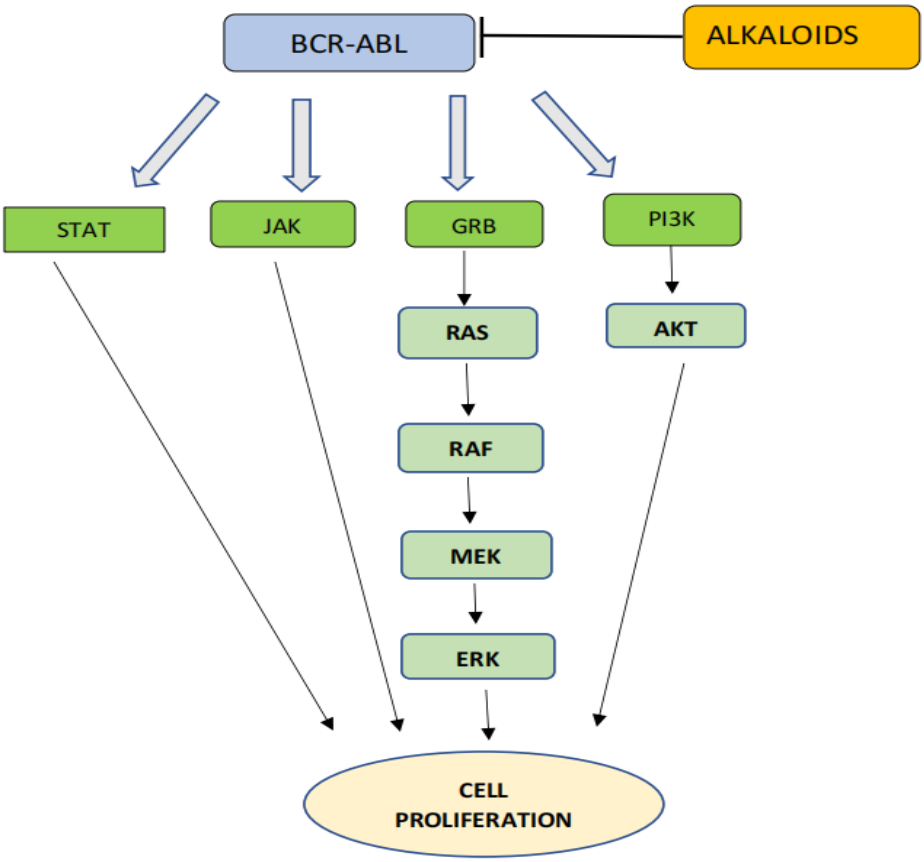


Figure 2.2: Inhibition of different signaling cascades using alkaloids that are activated by ABL-kinase.

2.3 Multidrug resistance in chronic myeloid leukaemia

BCR-ABL is constitutively active in CML suffering cells offered a justification for the beginning of the chronic phase and made target-oriented treatment possible. Patients with chronic phase CML have demonstrated to respond well and long-term to treatment with imatinib a derivative of a TKI (tyrosine kinase inhibitor). However, imatinib treatment results are impacted by CML progression. Imatinib was reported to have a full cytogenetic response rate of about 80% for patients having early chronic-phase, about 40% for patients with accelerated, and over 20% for the ones with blast. This profile may be caused by the fact that the cell is subject to genetic instability for a longer period of time before BCR-ABL becomes activated prior to the start of treatment.[15]

2.3.1 Process of resistance

Targeted therapy resistance can either be primary or it can be acquired. Characteristic of acquired resistance is as a recurrence following an initial response to therapy, whereas primary resistance is the absence of an acceptable reaction to therapy. Depending on the condition, the treatment targets, and the monitoring instruments, "satisfactory" response might signify different things. Primarily occurring resistance is typically less common than acquired resistance.

TKI resistance in CML can be caused by either BCR-ABL1dependent ("on target") or BCR-ABL1independent ("off target") resistance, which are fundamentally distinct from one another.

2.3.1.1. BCR-ABL1-Dependent Resistance

On point resistance occurs when the treatment target is directly altered to the point that it can no longer be properly suppressed. They include point mutations in the KD and, in the case of BCR-ABL1 overexpression, respectively, either qualitative or quantitative change of the target. The very first mutation identified in imatinib-resistant CML patients—and by far the most troublesome—was the presence of the amino acid threonine (T) instead for isoleucine (I) at place 315 (T315I) of the BCR-ABL1 protein.[16], [17]This replacement was assumed to completely abolish the interaction to drug.

In addition to T315I, a variety of further mutations causes amino acid to substitute in or close to the phosphate binding position, at others critical contact-binding areas among

imatinib and BCR-ABL1, within the C-, and in the loop that activates have been found in CML individuals who have imatinib resistance [18]. These mutations may cause regional or global conformational alterations which lower imatinib-binding affinity, which is considered to be a factor in resistance.

At the beginning of research on imatinib-tolerant CML cell lines, an excess of of the BCR-ABL1 transcripts and protein because of multiplication of the BCR-ABL1 fusion gene [16], [19]–[23] was in fact found. This indicated that the excessive expression of BCR-ABL1 might be an early event in the development of resistance and the progression of the illness in CML. As the disease progresses from chronic to blast, at which genetic instability is higher and cancer-causing is reduced, BCR-ABL1 excessive expression may be linked to resistance due to protein levels outweigh imatinib's inhibitory capacity. Additionally, it may be a sign that the disease is progressing because it reduces the effectiveness of the individual BCR-ABL1 inhibitor.

2.3.1.2. BCR-ABL1-Independent Resistance

As an alternative, resistance might arise due to processes unrelated to the target oncoprotein. Considering that 60–70% of individuals with an inadequate response to TKI treatment are negatives for alterations or transcript excess expression, BCR-ABL1-independent pathways are, in fact, the most common ones in CP patients. TKI resistance can occasionally arise despite successful on site inhibition, either as a result of signalling pathway reactivation downstream or as a result of the de novo activation of bypass parallel routes that takes over to maintain the oncogenic processes. Cancerous growth happens when oncogenes hijack important cellular pathways, such as the RAS or RAF or MEKor ERK process, the JAK2/STAT process, or when their constituents or upstream activators are activated directly.

2.4 Role of alkaloids in chronic myeloid leukemia leukemia

There is great potential for naturally occurring substances to treat many diseases, including cancer. Surgery and radiotherapy were the only treatment options available in the early 20th century, with a recovery rate of no more than 33% [24].

The last few decades have seen the discovery of a wide variety of cytotoxic agents using plants, but just a few of these have made it to clinical practise after successfully navigating the lengthy, expensive, bureaucratic, and selective procedure from their chemical detection to their efficacy in therapeutic treatment of cancer. Each of these substances has a history of accomplishments and setbacks, which have been detailed by several writers and are listed here from a historical, molecular, pharmacological, and clinical perspective. Plant-derived alkaloids and extracts have been implicated in the inhibition of oncogenesis. The creation of novel anticancer medications is a crucial tactic in the battle against cancer[15]. Currently, efforts are being made to develop novel anticancer drugs derived from natural sources. The sources of more than 60% of anti-tumor medications that have demonstrated great efficacy in clinical usage include plants, aquatic creatures, and microbes. Alkaloids have drawn a lot of interest due to their ability to influence the control of several biochemical pathways involved in cell division, cell cycle, and metastasis.[15]

2.4.1Anti CML alkaloids

Most alkaloids originate from simple precursors of amino acids. There are already about 20,000 compounds that cover different of chemical structures and functional groups.[25] The second-largest class of secondary metabolites that are formed by plants, animals, bacteria, and fungi are the alkaloids. Numerous alkaloids and their derivatives are still undergoing FDA-approved clinical trials. Alkaloids have many medicinal properties, including those that are antihistamine, antimalarial, anti-dilator, anti-cancerous, and antihyperglycemic. Phase I/II clinical trials evaluating quinine's effects suggest that it may be used safely in combination with a variety of other anticancer drugs to enhance the treatment of clinically resistant acute leukaemia. Cinchona alkaloid is derived from cinchona trees and contains the active compound quinine. Additionally, cinchonine has shown MDR-reversing properties in individuals having malignant lymphoid when

combined with a number of other medications.

Traditional and modern medicine have both utilised the anticancer effects of natural alkaloids to promote efficient overall cancer therapy. Plant alkaloids are the most promising as plant-based medicine research advances due to its shown efficacy and cost-effectiveness. NPs both prevent CML cell growth and trigger apoptosis, which results in cell death. The in vivo outcomes of several research have clearly demonstrated that NPs potently inhibit tumour development. NPs provide an endless source that makes a compelling alternative method against CML.

Leukaemia cells can be killed by plant extracts and their bioactive components in similar ways to how they influence animals. The most prevalent modes of action for these plant extracts and active components include inhibition of cell division, induction of cell cycle arrest, apoptosis, and dose- and time-dependent DNA damage. Perhaps these plants are the best option for the creation of suitable risk-reward research for the advancement of leukaemia treatment options based on clinical research looking into the consequences because they are more accessible to some populations are better suited when compared to chemotherapeutic drugs. Therefore, extra research is required to determine whether the extracts and their active ingredients from these medicinal plants have the potential to be used in chemo-preventive and chemotherapeutic therapy.

Alkaloids from plants have long been and will be a valuable source for cytotoxic chemotherapy and molecularly targeted cancer treatment. They occasionally, but more frequently, require thorough structural optimisation to enhance their pharmacokinetic, safety, and accessibility characteristics. Additionally, a thorough comprehension of the interactions between alkaloids and related signalling pathways will help in developing anticancer medications that are more efficient, selective, and less harmful by helping researchers better comprehend the mechanisms of action and pharmacokinetic performances.

As a second-generation TKI, nilotinib (TASIGNA®) is intended to outpace IM resistance brought about by a wide variety of mutation [26]. Nilotinib has three advantages over IMA: (1) it causes molecular reactions that are faster and deeper; (2) the site of attachment is more lipophilic, which increases its potency (it fits into the ATP-binding site); and (3) it can attach to the ABL kinase domain (KD) in inactive conformation[27] .

Nilotinib was shown to have a lower incidence of ischemic heart disease (5%), ischemic cerebrovascular disease (1.4%), and peripheral arterial disease (4.3%), compared to

IMA, after 6 years[28]. Nilotinib was reported to have greater rates of molecular response, a decrease of disease progress and CML-related mortality, and enhanced potential for treatment-free remission in a trial that monitored individuals with newly identified CML in chronic phase over 10 years or longer.[29]

Various alkaloids with there composition, properties and mechanism of action are described below:

Berbamine

Berbamine is a naturally occurring chemical with a molecular weight of 608.7 that comes from *Berberis amurensis*. It has antileukemic properties and works for both CML that is Gleevac sensitive and resistant. Inducing apoptosis through a caspase-3-dependent pathway, it has antiproliferative properties. It specifically prevents the formation of leukemic cells that are bcr/abl positive by only destroying bcr/abl-positive cells. The use of berbamine promotes cell growth by preventing JAK2 autophosphorylation, downregulating STAT3 pathway, and inactivating AKT pathway [30]. On the imatinib tolerant K562 cell line (K562/IR), berbamine (BBM) was put to the test both in vitro and in vivo. At 24 and 48 hours, the value of the IC50 was discovered as 17.1 and 11.1 M. By lowering survivin protein levels, BBM also caused apoptosis in CML cells.[12]

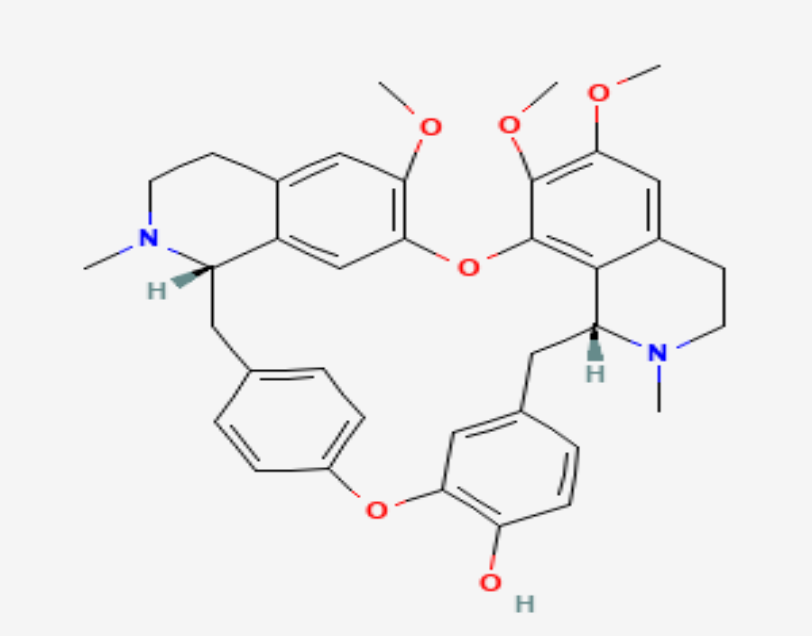


figure 2.3.Berbamine structure

Homocamptothecin

Homocampthothecin a synthetic derivative of camptothecin, demonstrated robust activity with an IC50 value of 11 nM, indicating its potential application in comparison to parent chemical camptothecin (IC50 57 nM), which is known to exhibit anti-CML activity.[31]

For more than 70 years, cepharanthine (CEP), a natural substance and licensed medication, has been used in Japan to cure a different acute and chronic staged diseases[32]. Additionally, protecting DNA from free radicals created by oxidative metabolism, CEP's scavenging actions. Because of how the medication impacts the cell cycle, cells are often stopped in the G1 and S stages. Leukemia cells and skin cancer cells have both been shown to undergo apoptosis as a result of CEP.

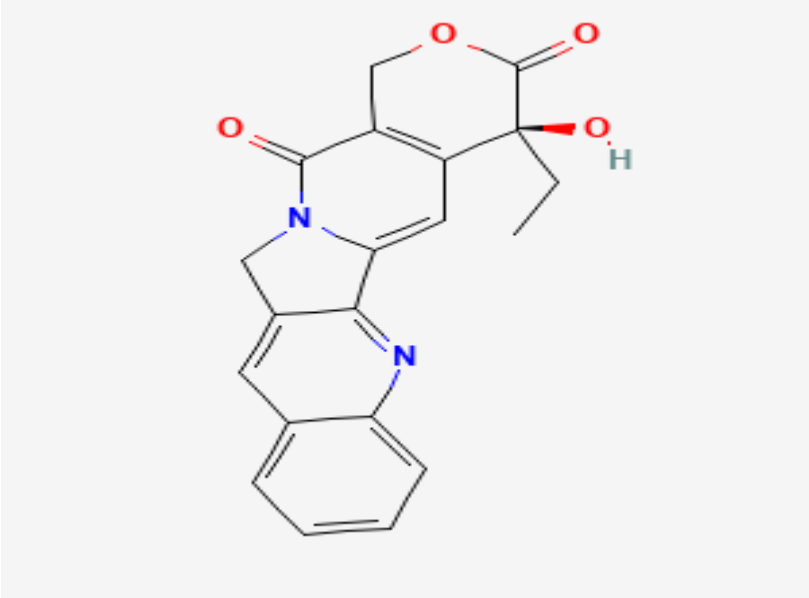


Figure 2.4. Camptothecin structure

Sanguinarine

Sanguinarine which is a benzophenanthridine alkaloid, is mostly extracted from Sanguinaria canadensis and is described as a "natural product". In preliminary pre-clinical investigations using animal models, both in vivo and in vitro, SNG has demonstrated anticancer promise. This is because a number of tumors, including hematological malignancies, have been well-documented to induce apoptosis and anti-angiogenic activities. SNG is not damaging to healthy cells, indicating that it has promise as an anticancer drug. Through both internal and extrinsic apoptotic mechanisms, SNG has been proven to cause cell lysis. The formation of reactive oxygen

species by SNG, which causes oxidative stress and degrade the cancer-causing cells, has been shown to inhibit more than 70% of tumor development. SNG also has lethal effects by inhibiting the activation of several signaling cascades in a variety of cancer cell types. Sanguinarine (SNG) was demonstrated in prior research to inhibit carcinogenic action in different of cancer cell lines. SNG's function in initiating intrinsic apoptosis, promoting the formation of reactive oxygen species, and causing DNA degradation were the main anti-cancer strategies.

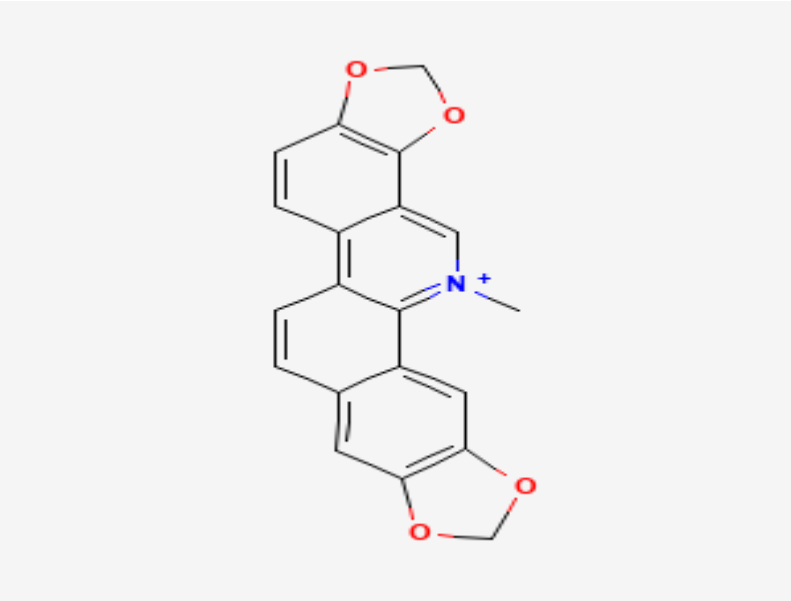


figure 2.5. Sanguinarine structure

Many of the alkaloids which are approved by FDA that are currently on the market are derived from plants. Alkaloids are significant chemical compounds function as abundant sources of bioactive chemicals for the development of drugs with anticancer characteristics.. Some of them have demonstrated varying degrees of success over the past five years in various stages of clinical trial.[25]

Cepharanthine

For over 70 years, cepharanthine, a natural substance and licenced medication, has been used in Japan to cure a range of acute and chronic illnesses. Of genus Stephania, one of the largest genera in the family Menispermaceae, is where CEP is isolated from plants. More than 600 distinct alkaloids have been extracted from the Stephania genus, and extracts of S. cephalantha were used to characterise roughly 40 different alkaloids[32]. In vitro, CEP inhibits the growth of several cancer cell lines. Because of how the drug

impacts the cell cycle, cells are often stopped in the G1 and S stages. Leukaemia cells and skin cancer cells are only two of the cell types in which CEP has been detected to induce apoptosis.[32]

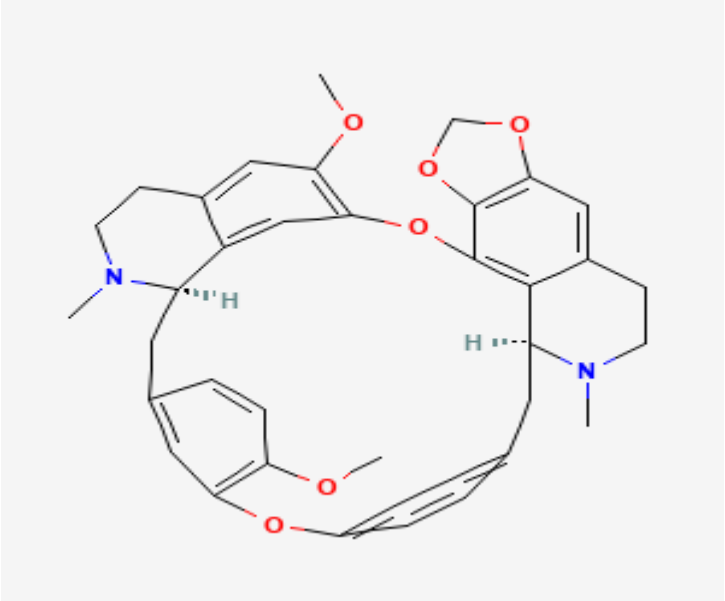


Figure 2.6. Cepharanthine structure

Our knowledge of the molecular cause of cancer, the categorization of tumours, and currently the the clinic's treatment of cancer patients have all considerably improved as a result of the use of methods to efficiently bioinformatics-based data mining and molecular tests. Numerous bioinformatics-based methods exist for extracting information from data generated by high-throughput information-rich techniques. These techniques include genomic, microarray gene (gene chip), epigenetic, genome architecture, transcriptomics, proteomics, all of which have contributed significantly to the cancer's molecular targets are identified and the clarification of molecular pathways.[25]

Using computational methods like quantitative structure-activity relationships (QSAR) and quantitative structure-properties relationships (QSPR), structure-based pharmacophore modelling and computational methods may be able to shed light on the nature of ligand-binding areas in various targets as well as identify new interaction sites and new ligands with effective affinity for ligand-receptor binding.[25]

2.4.2. Designing of anticancer drugs based on natural alkaloids

Traditional and modern medicine have both utilised the anticancer capabilities of natural alkaloids to promote cost-effective overall cancer therapy. Investigating a natural material as a cancer therapy is a promising course of action [33]. Plant alkaloids have the most potential as plant-based medicine research advances due to its demonstrated efficacy and cost-effectiveness. A wise choice and holistic strategy for choosing the molecule (individual or group), plants source, and plant component are crucial for the identification of novel natural product-based chemopreventive drugs [34], [35]

The challenge of obtaining natural substances becomes difficult though under the case of extreme pressure on plant-based resources with many plant resources falling into the categories of "Rare" or "Endangered"[35] . However, the industrial scale harvesting of new alkaloid compounds and biopharmaceuticals from various in-vitro procedures can be a sustainable approach to anticancer chemicals.

In recent years, several cancer medications have been created; however, these medications have adverse effects and can cause patients to become resistant to them gradually[36] . As a result, it is challenging to create a chemical-based treatment that can effectively discriminate between normal and tumour cells. Given the negative effects of synthetic pharmaceuticals, it has been observed that the use of plant-based medications has increased in both developed and developing nations [37]mostly because of their effectiveness, safety, lack of side effects, accessibility, and acceptance.

2.4.3. Treatment restrictions with alkaloids

Alkaloids' pharmacokinetic and side effect characteristics serve as therapeutic limits[38]

(i) Additional haematological effects, such as myelosuppression. In the initial days following administration, leukopenia happens. Mild and temporary thrombocytopenia is reported [39]

(ii) Vomiting and nausea [40].

(iii) Extravasation can cause tissue injury, excruciating pain, and severe inflamation[41].

(iv) Alopecia, a characteristic partial condition [42].

(v) Neurotoxicity - High dosages or extended therapy may raise the risk of neurotoxicity in certain alkaloids, such as vinca alkaloids. Neurotoxicity can happen within a few days after therapy begins, and recovery often takes place weeks or months after treatment is stopped. Vegetative neuropathy, including urine retention, hypotension at orthostatic and constipation, may be brought on by high dosages.

(vi) Tumour lysis syndrome, which causes electrolyte disbalances or abrupt renal failure, might develop from the cell lysis caused by cytotoxic treatment. Leukaemias, high-grade lymphomas, and myeloproliferative disorders are among the tumours most likely to have this characteristic, as are tumours with a high rate of proliferation and noticeable tumour bulk. Patients who already have kidney failure, mainly ureteral blockage, might be at greator risk.

(vii) Alkaloids also have a low water solubility and limited bioavailability, which makes it difficult to obtain effective therapeutic concentrations in the tumour target. novel approaches are thus required to boost their bioavailability, including structural alterations, the development of nanotechnologies, and novel therapeutic targets transport systems [43].

CHAPTER 3
METHODOLOGY

3.1 Data collection

Twenty different alkaloids were chosen with anti-leukemic properties from various sources, including PubMed, Google Scholar, Web of Science, Scopus, etc. The SDF 3D files for all the chemical structures of various alkaloids were obtained from the PubChem database. ABL-kinase's PDB structure was downloaded from the Protein Data Bank website.

3.2 Receptor and ligand preparation

The BIOVIA discovery studio was used to prepare the target protein ABL-kinase. Water molecules and hierarchy were removed from the protein when it opened BIOVIA and observed the hierarchy. The ABL-kinase protein was then given polar hydrogen atoms, and the file was then stored in PDB format.

For docking, the PyRx virtual screening tool was employed. It is a multiple ligand docking programme that includes embedded versions of AutoDock, Vina Wizard, AutoDock Wizard, and Open Babel to make it simple to convert ligands from SDF file to PDB format. Using the PyRx screening tool, protein was imported and transformed from PDB to PDBQT format by selecting "Make macromolecule" from the AutoDock menu. After adding the ligand to PyRx, click "Minimise All" to reduce all of the energy. Later all the ligands were converted to PDBQT format.

3.3 Implementing AutoDock Vina for Molecular Docking

The entire molecule will be covered by the grid box when you navigate to Vina Wizard, click on Start, and then pick the ABL-kinase protein and ligands. The grid was created automatically, and after being filled with dots that covered the whole inner cavity of the receptor and the ligand, it was clicked forward. After docking was finished, the scores were entered into an Excel spreadsheet by selecting "Save as Comma separated values." The conformation of the ligand with the greatest binding affinity among all the

conformations formed was then determined by watching the display in AutoDock, which was followed by the determination of the best score. The ligand's display was then converted to a molecular surface, and a PDB file was then saved.

3.4 Swiss ADME assessment

For assessing various factors like absorption, distribution, and excretion of ligands an online programme Swiss ADME was used. Knowing about these factors gives better understanding for ligand’s solubility, physiochemical and pharmacokinetics properties. Data collected from Pub Chem was loaded in smiles format in Swiss ADME programme.

CHAPTER 4

RESULT

Structure of Target protein [ABL-Kinase]

The original 3-D structure of ABL-kinase is shown in figure4.1 without minimising energy, and figure 4.2 depicts structure of ABL-kianse after minimising energy, eliminating water molecules and hetatm.

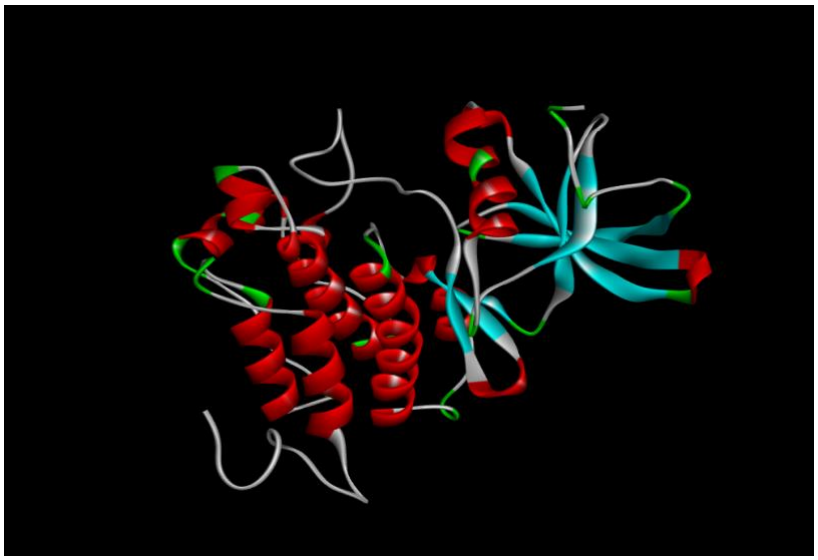


figure 4.1. Novel structure of ABL-kinase before removing all water molecules and hetatms

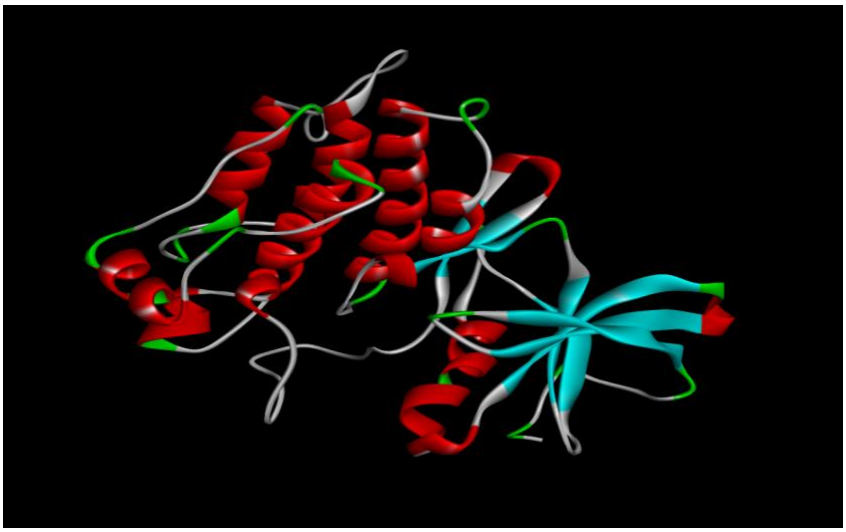
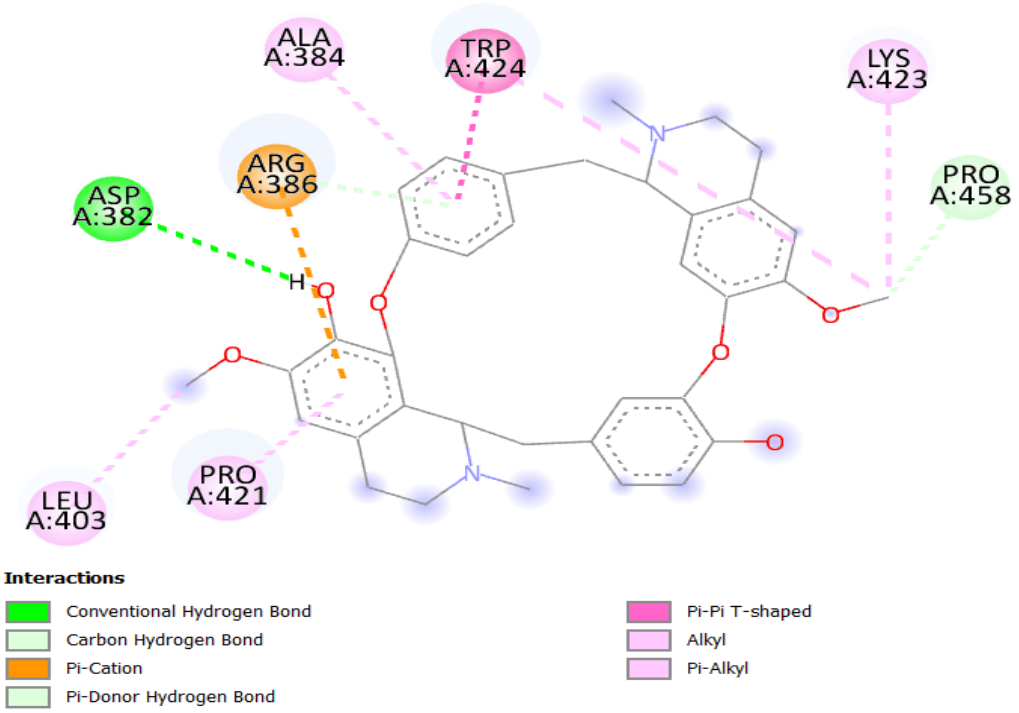


figure 4.2. 3-D Structure pf ABL-kinase after removing all water molecules and hetatms

4.1 Interaction between ABL-kinase and ligands

In this study 20 alkaloids were chosen from various sources showing anti leukemic property. Among those 20 alkaloids selected, Curine was found to have the highest ABL-kinase binding affinity, followed by Berbamine and Cepharanthine at -9.1. Table 4.2 lists other 10 alkaloids having high ABL-kinase binding affinity along with their PubChem CIDs.



.figure 4.3. 3-D image showing binding of ligand Curine and receptor ABL-kinase.

The hydrophobic interactions between Curine and ABL-kinase are depicted in Figure 4.3 as one normal hydrogen bond, one bond between carbon hydrogen , one Pi-donor hydrogen bond, and various others.

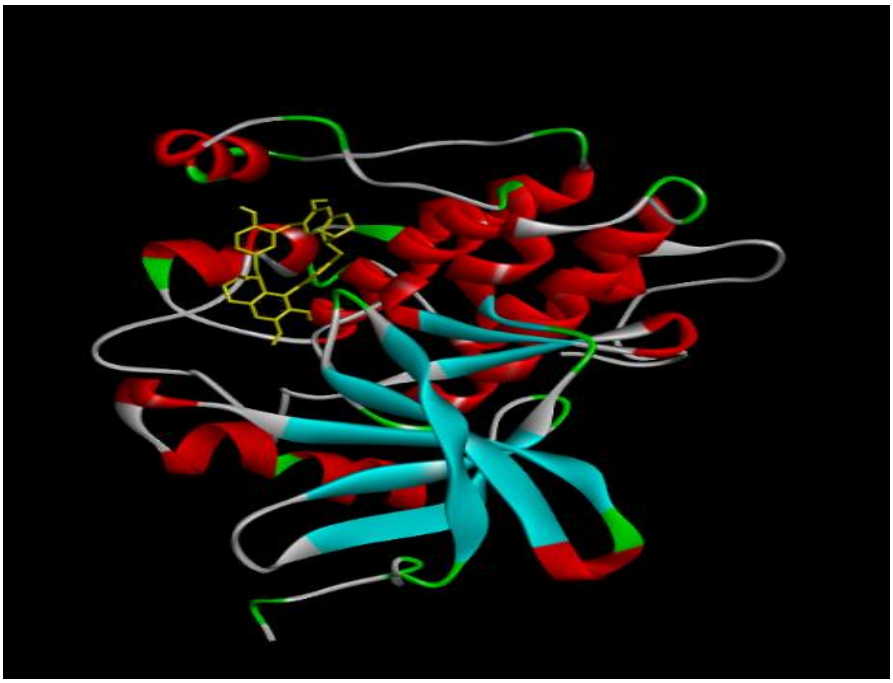


figure 4.4. All interaction between Curine with ABL-kinase

S.No.	PubChem CID	Name of alkaloid	Binding affinity(Kcal/mol)
1	253793	Curine	-9.6
2	275182	Berbamine	-9.1
3	10206	Cepharanthine	-9.1
4	5154	Sanguiuarine	-8.5
5	10666346	Homocamptothecin	-8
6	24360	Camptothecin	-7.7
7	179169	Ancistrotectorine	-7.6
8	3034034	Quinine	-7.5
9	159999	Crebanine	-7.4
10	276389	Harringtonine	-7.3
10	644241	Nilotinib	-10.1

Table 4.2. Various alkaloids with their binding affinity (Kcal/mol) with abl-kinase

4.2 Swiss ADME assessment of Curine

In ADME acronym (A represents absorption, D for distribution, M for metabolism, E for excretion) a group of variables that are examined in order to learn more about a drug's physicochemical composition, pharmacokinetics, lipophilicity, water solubility, and possible efficacy. Analysing these variables offers useful knowledge regarding the effectiveness and performance of the medication. Online tool SwissADME (http://www.swissadme.ch) is used to evaluate these properties for small-molecule ligands. The ligand-protein interactions are represented in this programme through data imported in the SMILES format. SwissADME normally obtains its SMILES data from PubChem.

Based on pharmacokinetics data, Curine is highly absorbable in the gastrointestinal tract, according to pharmacological data. Log S value is -9.44, skin permeability is -5.66 cm/s, and the bioavailability score is 0.55, all of which indicate that the substance is poorly soluble in water.

Table 4.1: SWISS-ADME assessment of Curine

Physicochemical properties	
Molecular weight	594.70 g/mol
Number Hydrogen bond acceptors	8
Number Hydrogen bond donors	2
Molar Refractivity	177.14
Water Solubility	
Log *S* (SILICOS-IT)	-9.44
Solubility	2.17e-07 mg/ml ; 3.66e-10 mol/l
Class	Poorly soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
skin permeation	-5.66 cm/s
Druglikeness	
Bioavailability Score	0.55

CHAPTER 5
DISCUSSION

Cancer continues to be the leading global killer traditional nonsurgical cancer therapy regimens like chemotherapy and radiation have been incredibly difficult for decades because to the lower rate of survival, re-ocurrence of cancer, morbidity, and poor diagnosis prediction of the illness. In chronic myeloid leukaemia TKIs successfully suppressed wild-type BCR-ABL; however, BCR-ABL mutations and post-treatment upregulation of drug efflux proteins reduced their effectiveness. TKI treatment is not therapeutic, and persistent adverse effects are linked to long-term TKI exposure. A unique option for CML patients, treatment-free remission is only possible for a tiny percentage of individuals. It is apparent that new therapeutic choices need to be researched because there are still several unmet clinical needs. As our knowledge of the biology of CML has increased, several different strategies have been examined. To solve the issue, several new substances are now being studied in both preclinical and clinical settings. Few people can safely cease their medication without the possibility of relapsing. Currently, plant-based medications are dominating the cancer therapy industry. Due to alkaloids' higher selectivity, greater efficiency, and lesser toxicity, there have been several investigations on their anticancer activity. The methods through which alkaloids work are extremely intricate and distinctive for each alkaloid. Natural products (NP) offer an alternative, efficient, and cost-effective design for CML treatment therefore different methods are required to create new BCR-ABL inhibitors. CML cells can be transformed into erythroid, monocyte, lineages by a number of NPs. The potency of NPs to reduce tumour development has been amply demonstrated by in vivo data. In conclusion, NPs provide an endless source that makes a compelling alternative tactic to tackle CML.

CHAPTER 6
CONCLUSION

In the decades-long hunt for possible anticancer drugs from natural products, tremendous progress has been achieved thanks to the discovery of nature's bounty in the form of a wide variety of alkaloids with targets and modes of action compatible with the many tumor forms that affect human civilization. The result was made possible by searching the trees for natural compounds with anticancer qualities; nevertheless, their application in human cancer treatment was constrained owing to cytotoxicity and other adverse effects.

Even though certain natural substances have distinctive anticancer effects, their application in clinical practise is not feasible because of their physico-chemical characteristics (such as their toxicity or restricted absorption). On the other hand, naturally occurring secondary metabolites from plants are frequently great candidates for drug discovery. As a result, one clever strategy to improve these more promising chemicals' anticancer effect is to change the structure of them. In order to enhance effectiveness on cancer cells and circumvent any natural availability and solubility limitations, extensive structural modification of the parent molecule is still being investigated.

TKIs were initially used to compete for the ATP binding site in CML, which is brought on by the Philadelphia chromosome, but their effectiveness has declined as a result of BCR-ABL mutations and multidrug resistance. Alkaloids are a class of natural products that, when combined with TKIs, have the ability to reverse MDR by triggering apoptosis, reducing cell proliferation, and arresting cell cycle.

As a result, alkaloids like Curine and Berbamine, which have a very high affinity for ABL-kinase and can be combined with other TKIs to increase TKI sensitivity while also having fewer side effects and being more suitable for use, are the best options for treatment. However, more study on alkaloids and other natural products is required to better characterize their antileukemic activity and to create novel anti-cancerous medications with comparatively low resistance, toxicity, and efficacy.

While high-value medicinal plants are under pressure and their biodiversity is at risk due to the demand for plant-derived drugs, the exploitation of these agents must be controlled in order to meet demand and be sustainable. The synthesis of valuable plant metabolites is fortunately being developed utilising innovative biotechnological techniques and environmentally friendly alternative ways.

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CANDIDATE'S DECLARATION

I, **Pratibha Yadav [2K21/MSCBIO/33],** student of **M.Sc. Biotechnology,** hereby declare that the project Dissertation titled **"Molecular docking of various alkaloids against ABL-kinase for anti-chronic myeloid leukemic property"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirements for the award of the degree of Master of Science, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateships, Fellowship or other similar title or recognition.

Title of the Paper: "Molecular docking of various alkaloids against ABL-Kinase for anti- chronic myeloid leukemic property"
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PRATIBHA YADAV

[2K21/MSCBIO/33]

Place: Delhi

Date: 30-05-23

DEPARTMENT OF BIOTECHNOLOGY

DELHI TECHNOLOGICAL UNIVERSITY

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CERTIFICATE

I, hereby certify that the Project Dissertation titled, **"Molecular docking of various alkaloids against ABL-kinase for anti-chronic myeloid leukemic property"** which is submitted by, **Pratibha Yadav [2K21/MSCBIO/33],** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date: 30-05-23

30.05.23

Prof. YASHA HASIJA

SUPERVISOR

08/06/2023

Prof. Pravir Kumar

Head of Department

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Pratibha.

PRATIBHA YADAV