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Molecular Docking Of Various Alkaloids against ABL-Kinase for Anti-Chronic Myeloid Leukemic Property

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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.

Index Terms*—ABL kinase, TKI, Alkaloids, Multi-drug resistance, Molecular docking.

I. INTRODUCTION

Chronic myeloid leukemia is myeloproliferative neoplasm caused by the reciprocal translocation of chromosomes 9 and 22 [t (9;22)], which results in the formation of the Philadelphia chromosome. This translocation results in the formation of the fusion gene 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 abnormal chromosome in chronic myeloid patients almost a century ago; this chromosome is now 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].

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

Philadelphia chromosomes are formed in CML patients by genomic recombination of the ABL gene on chromosome 9's long arm and the BCR gene on chromosome 22's long arm [8]. The ABL gene has 11 exons, a tyrosine kinase domain, a DNA binding domain that interacts with the nucleus, an acting binding domain that interacts with the cytoskeleton in the cytoplasm, and three sarcoma homology domains (SH1, SH2, and SH3) [9].

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 [9].

Both the ABL and BCR genes have different breakpoint regions [10]. 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[9]. E19a2 micro-transcript produces 230kDa protein [8].

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

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resistance to apoptosis.

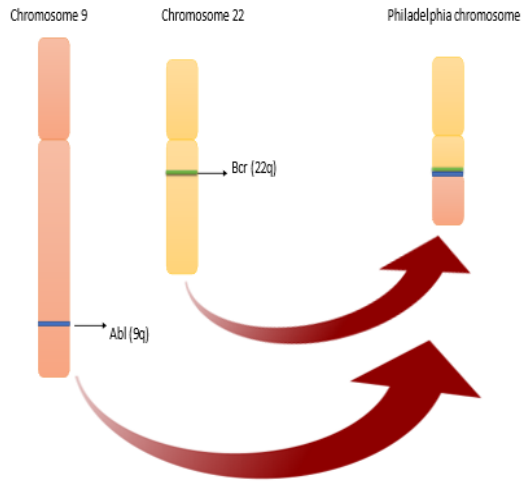

Figure 1: Showing translocation between chromosome 9 and chromosome 22 forming Philadelphia chromosome.

Bcr-abl codes for tyrosine kinase enzyme that further activates various pathways involved in cell survival and cell division, including the RAS, MAPK, JAK-STAT, and PI3K pathways [11]. Numerous connections between Ras and Bcr-Abl have been identified. Since then, multiple BCR-ABL-positive cell lines and primary CML cells have been found to have activation of Stat transcription factors (Stat1 and Stat5), and Stat5 activation seems to play a role in malignant transformation. 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[12]. 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[12]. 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.[12]

The new finding that Bcr-Abl causes the degradation of the inhibitory proteins Abi-1 and Abi-2 by the proteasome may be the first sign of yet another mechanism by which Bcr-Abl causes cellular change. 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.[12]

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.

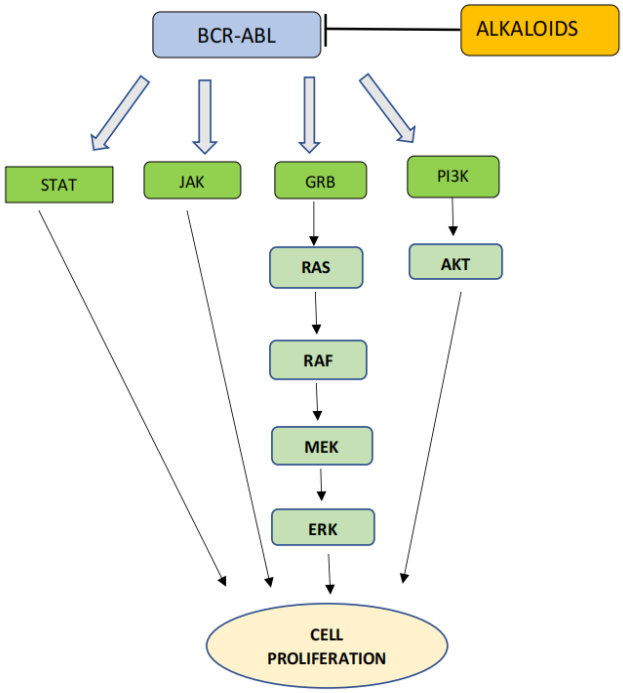

Figure 2: Inhibition of different signaling cascades using alkaloids that are activated by ABL-kinase.

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% [13].

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. 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.

Most alkaloids originate from simple precursors of amino acids. There are already about 20,000 compounds that cover a wide range of chemical structures and functional groups.[14]

The second-largest class of secondary metabolites that are produced by plants, animals, bacteria, and fungi are the alkaloids. Numerous alkaloids and their derivatives are still

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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 patients having malignant lymphoid disease when combined with a number of other medications.

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 development 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 [15]. 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.[11]

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.[16]

For more than 70 years, cepharanthine (CEP), a natural substance and licensed medication, has been used in Japan to cure a variety of acute and chronic diseases[17]. Additionally, protecting DNA from free radicals created by oxidative metabolism, CEP's scavenging actions. In vitro, CEP inhibits the growth of several cancer cell lines, T-cell lines, and peripheral mononuclear cells. 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.

Sanguinarine 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 activity in a variety of cancer cell lines. SNG's function in initiating intrinsic apoptosis, promoting the production of reactive oxygen species, and causing DNA degradation were the main anti-cancer strategies.

Many of the FDA-approved alkaloids that are currently on the market are derived from plants. Alkaloids are significant chemical compounds which act as rich reservoirs of bioactive molecules for anticancer properties drug discovery. Some of them have demonstrated varying degrees of success over the past five years in various stages of clinical trial.[14]

Our knowledge of the molecular cause of cancer, the categorization of tumours, and currently the management of cancer patients in the clinic have all considerably improved as a result of the use of high-throughput bioinformatics-based data mining approaches 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, and ribosome profiling data, all of which have contributed significantly to the identification of molecular targets in cancer and the clarification of molecular pathways.[14]

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 sites in various targets as well as identify new interaction sites and novel ligands with effective ligand-receptor binding affinity.[14]

II. METHODOLOGY

A. 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.

B. Receptor and ligand preparation

For performing molecular docking ABL-kinase structures were prepared using AutoDock Tools (ADT). Structures were modified with polar hydrogens, ADT was used to remove any water molecules that were attached to it, and the resulting receptors were saved in the form of PDBQT file. Different alkaloids were converted from SDF to PDB format first, then to PDBQT format with the help of ADT.

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C. Implementing AutoDock Vina for Molecular Docking

The prepared receptor and ligands were molecularly docked using the AutoDock Vina Software. Discovery Studio Visualizer was used to create images of protein-ligand complexes.

D. 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.

III. RESULT

A. 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, equal to Nilotinib at -9.6, followed by Berbamine and Cepharanthine at -9.1. Table 1 lists other 10 alkaloids having high ABL-kinase binding affinity along with their PubChem CIDs.

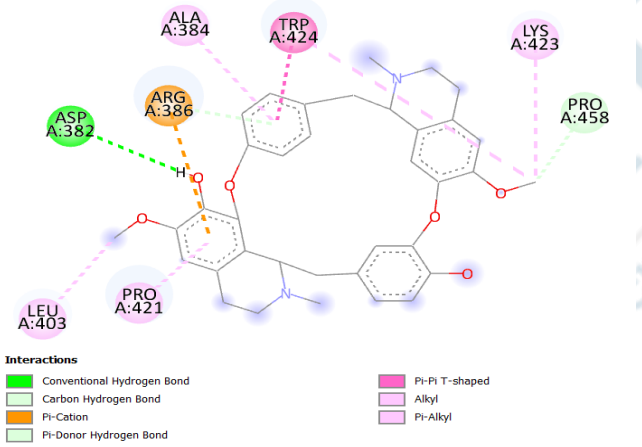

Figure 3: 3-D image showing binding of ligand Curine and receptor ABL-kinase.

The hydrophobic interactions between Curine and ABL-kinase are depicted in Figure 3 as one conventional hydrogen bond, one carbon hydrogen bond, one Pi-donor hydrogen bond, and various others.

B. Swiss ADME assessment of Curine

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.

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. These plants may be the best option for the development of adequate risk-reward studies for the potential treatment of leukaemia based on clinical studies that investigate the side effects because they are more accessible to some populations and better suited when compared to chemotherapeutic drugs. Therefore, more 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.

Figure 4: All interaction between Curine with ABL-kinase

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Table.1 Various alkaloids with their binding affinity (Kcal/mol) 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	-7.6
7	179169	Ancistrotectorine	-7.6
8	159999	Crebanine	-7.4
9	3034034	Quinine	-6.6
10	644241	Nilotinib	-9.6

IV. 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 low survival rate, morbidity, recurrence of cancer, 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.

V. 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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