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"IN SILICO OF PHYTOCONSTITUENTS FROM *ASHWAGANDHA, GUDUCHI, SHATAVARI, PUNARNAVA AND HARIDRA* AS POTENTIAL ANTI-LEUKEMIC AGENTS"

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ABSTRACT

Background: Leukemia continues to pose a major haematological health challenge worldwide, arising from the uncontrolled clonal proliferation of abnormal white blood cells within the bone marrow. Resistance to tyrosine-kinase inhibitors and the systemic toxicity associated with conventional chemotherapy have driven a growing interest in plant-derived molecules as safe adjuvant or alternative therapeutic leads. **Materials & Methods:** Molecular docking was done with AutoDock Vina on Mcl-1 (PDB: 2HYY) and Protein Kinase C alpha (PDB: 4TWP).TheADME properties were checked using SwissADME,and target prediction was do ne using SwissTargetPrediction. **Observation and Results**: All 86 compounds fully satisfied Lipinski's rule of five with zero violations, indicating favourable oral drug-likeness across the entire library. Ashwagandha withanolides, particularly Withanolide P (−9.8 kcal/mol), Guduchi's berberine (−8.3 kcal/mol) and Punarnava's Diffusarotenoid (−9.6 kcal/mol against the resistant mutant) emerged as the strongest binders. SwissTargetPrediction consistently flagged Protein Kinase C alpha, induced myeloid leukemia cell differentiation protein Mcl-1, and tyrosine-protein kinase ABL1 as shared probable targets across all five plants**. Discussion:** These findings lend computational support to the traditional use of these Ayurvedic herbs and nominate specific withanolides, alkaloids and boeravinones as promising drug-like leads against both wild-type and drug-resistant BCR-ABL1-driven leukemia, warranting further in vitro and in vivo validation. **Conclusion:** This study reinforces the potential of classical Ayurvedic herbs in anti-leukemic drug discovery using computational screening strategies.

Keywords: Chronic Leukemia, Phytochemicals, Ayurvedic Plant, In silico

1.Introduction

Cancer continues to rank among the leading causes of mortality worldwide, and within haematological malignancies, leukemia — cancer of the blood-forming tissue of the bone marrow — accounts for a substantial

share of the global disease burden. According to GLOBOCAN 2022 estimates of the International Agency for Research on Cancer, leukemia is diagnosed in close to half a million people every year, making it the thirteenth most commonly diagnosed cancer worldwide [1]. Leukemia arises from clonal, uncontrolled proliferation of abnormal leukocyte precursors within the bone marrow, and its subtypes differ considerably by age, sex and geography, with acute myeloid leukemia and chronic lymphocytic leukemia dominating in adults across most regions [2]. Traditional small-molecule drug discovery, built on iterative cycles of synthesis, isolation and biological testing, remains slow and resource-intensive. In silico methods — computational prediction of a molecule's pharmacokinetic behaviour, likely biological targets and binding affinity to a receptor of interest — have therefore become an efficient first-pass filter that allows large phytochemical libraries to be prioritised before committing to costly and time-consuming wet-laboratory validation.

Among the leukemia subtypes, chronic myeloid leukemia (CML) is defined almost universally by the Philadelphia chromosome translocation , which fuses the BCR and ABL1 genes to generate a constitutively active BCR-ABL1 tyrosine kinase that drives unchecked myeloid cell proliferation and resistance to apoptosis [3]. Tyrosine kinase inhibitors such as imatinib, which binds the wild-type ABL1 kinase domain in an inactive conformation, transformed CML from a rapidly fatal disease into a manageable chronic condition [4]; however, gatekeeper mutations — most notably the threonine-to-isoleucine substitution at position 315 (T315I) — distort the imatinib-binding pocket and confer clinically significant drug resistance, necessitating alternative inhibitor scaffolds such as axitinib that can accommodate the mutant conformation [5]. It is against this backdrop of persistent drug resistance that Ayurveda's long-standing Rasayana (rejuvenative) herbs merit renewed scientific attention. Ashwagandha (Withania somnifera) is rich in withanolides, most notably withaferin A, which has been reported to interact with p53, NF-κB and the catalytic site of BCR-ABL itself to induce apoptosis and cell-cycle arrest in cancer cells, including CML models [6]. Guduchi (Tinospora cordifolia) is a Menispermaceae climber whose alkaloids — berberine, magnoflorine and palmatine among them — and diterpenoid lactones are documented for immunomodulatory and antiproliferative activity. Shatavari (Asparagus racemosus), the traditional 'Queen of Herbs', yields steroidal saponins from its tuberous roots with reported antiproliferative effects in several experimental cancer models. Punarnava (Boerhavia diffusa) is a principal source of rotenoids called boeravinones and the alkaloid punarnavine; ethanolic root extracts of Punarnava have been shown to arrest the cell cycle and induce apoptosis in cervical cancer cells in vitro [7]. Haridra (Curcuma longa), finally, is the source of curcumin and related curcuminoids, whose ability to suppress BCR-ABL1 signalling, downregulate microRNA-21, and re-sensitise imatinib-resistant CML cell lines has been the subject of an extensive and growing body of literature.

Building on this ethnopharmacological foundation, the present study was undertaken to computationally screen the phytochemical repertoire of these five Ayurvedic plants against leukemia-relevant protein targets. Specifically, the physicochemical and drug-likeness properties of each phytoconstituent were assessed using SwissADME, a validated, freely accessible web tool that applies Lipinski's rule of five and related medicinal-chemistry filters to gauge the likelihood of oral bioavailability [8]. The probable human protein targets of each phytochemical were independently predicted using SwissTargetPrediction, a reverse-screening server that compares a query molecule against a curated library of bioactive compounds with experimentally confirmed targets [9]. Finally, molecular docking was performed against the crystal structures of the wild-type BCR-ABL1 kinase domain (PDB: 2HYY) and its clinically important, imatinib-resistant T315I mutant (PDB: 4TWP) to estimate binding affinity and pose plausibility. Taken together, this integrated ADME–target prediction–docking workflow was designed to identify phytochemicals from Ashwagandha, Guduchi, Shatavari, Punarnava and Haridra that possess genuine, structurally-grounded potential to interfere with the kinase and anti-apoptotic targets that sustain leukemic cell survival, including in the setting of tyrosine-kinase-inhibitor resistance.

2. Materials and Method

The present investigation followed a structured in silico workflow comprising literature-based selection of plant constituents, ligand and target protein preparation, molecular docking, ADME/drug-likeness evaluation and target prediction, as summarised below.

2.1 Drug-likeness / ADME screening

The SMILES string of every phytochemical was individually submitted to SwissADME (http://www.swissadme.ch) [8] to compute molecular weight, the number of hydrogen-bond donors and acceptors, and the consensus lipophilicity value (iLOGP), and to assess compliance with Lipinski's rule of five [10]. Under this rule, an orally bioavailable drug candidate is expected to have a molecular weight below 500 Da, not more than five hydrogen-bond donors, not more than ten hydrogen-bond acceptors, and a calculated logP not exceeding 5; compounds recording more than one violation of these criteria were flagged as poor oral drug candidates.

2.2 Target prediction

The same set of SMILES was submitted to SwissTargetPrediction (http://www.swisstargetprediction.ch) [9], which performs a 2D- and 3D-similarity-based reverse screen against a curated library of bioactive molecules with experimentally established targets, in order to shortlist the most probable human protein targets for each phytochemical.

2.3 Receptor structure preparation

Two crystal structures of the Abelson (ABL1) tyrosine kinase domain were retrieved from the RCSB Protein Data Bank. The wild-type kinase domain in complex with imatinib (PDB ID: 2HYY) [4] was used to represent the classical BCR-ABL1 target engaged by first-line CML therapy, while the imatinib-resistant T315I gatekeeper mutant in complex with axitinib (PDB ID: 4TWP) [5] was used to represent a clinically significant resistant genotype. Both structures were stripped of co-crystallised water molecules and the native small-molecule ligand, and polar hydrogens and Kollman partial charges were added prior to docking.

2.4 Molecular docking

All 86 phytochemicals were docked against both receptor structures using AutoDock Vina [11], with the search space centred on the co-crystallised ligand-binding pocket of the respective structure. For each ligand–receptor pair, the lowest (most favourable) binding-affinity pose was retained, together with its associated upper- and lower-bound root-mean-square deviation (RMSD) values, as a measure of pose reproducibility.

2.5 Data compilation and analysis

Docking scores, ADME parameters, and SwissTargetPrediction outputs were compiled plant-wise and analysed using Python (pandas library) to identify the highest-affinity phytochemicals per plant, per receptor, and the protein targets shared across the five plants.

2.6 Comparative Ayurvedic Pharmacological Profile

Drug Name	Latin Name	Family	Rasa	Guna	Virya	Doshaghnata	Karma
Ashwagandha	Withania somnifera	Solanaceae	Tikta, Kashaya, Katu	Laghu, snigdha	Ushna	Vata-Kaphahara	Rasayana Brimhaneeya
Guduchi	Tinospora cordifolia	Menispermaceae	Kashaya	Laghu, Snigdha	Usna	Tridoshaghna	Rasayan Jvaraghna Raktashodhaka
Shatavari	Asparagus racemosus	Asparagaceae	Madhura Tikta,	Guru, Snigdha	Sheet	Vata-Pittashamaka	*Rasayana Stanyajanana* Hridya

Punarnava	Boerhavia diffusa	Nyctaginaceae	Tikta, Kashaya Madhura	Laghu, Tikshna	Ushna	Tridosha	Shothahar Rasayana
Haridra	Curcuma longa	Zingiberaceae	Katu Tikta	Laghu Ruksha	Ushna	Kapha-Pittahara	Vranashodhana Kusthaghna

3. Observation

Plant- Ashwagandha (*Withania somifera)*

Chemical constituent		Protein	Binding Affinity	RMSD Value	Lipinski rule		Target Predication
(+/-)-Karachine	3.372	2HYY 4TWP	-8.6 -9.4	3.372 3.769	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	141.212 4 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Hygrine		2HYY 4TWP	-9.4 -3.8	9.733 30.943	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	4706 4 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Withanolide D		2HYY	-5.3 -9.1	51.955	Molecular weight #H-bond	4706 4 n/d 0	Protein Kinase C alpha type ,Protein Kinase

	4TWP		30.943	acceptors #H-bond donors iLOGP Lipinski #violations		C (general - multiple isoforms listed)
Withaferin A	2HYY 4TWP	-8.4 -8.7	7.474 35.709	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	470.64 n/d	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Withanolide E	2HYY 4TWP	-9.2 -8.9	43.316 3.813	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	486.674 n/d	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Withanolide P	2HYY 4TWP	-9.8 -8.7	63.899 26.489	Molecular weight #H-bond acceptors #H-bond donors iLOGP	454.654 n/d	Protein Kinase C alpha type ,Protein Kinase C (general - multiple

				Lipinski #violations		isoforms listed)
Withanolide L	2HYY 4TWP	-9.7 -5.3	40.928 37.616	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	452.5854 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Tropine	2HYY 4TWP	-5 -8.1	19.357 2.985	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	141.2124 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
(2R)-2-[(1S)-1-[(8R,9S,10R,13S,14R,17S)-14,17-dihydroxy-10,13-dimethyl-1-oxo-4,7,8,9,11,12,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-1-hydroxyethyl]-4,5-dimethyl-2,3-dihydropyran-6-one	2HYY 4TWP	-7.5 -4.7	64.057 20.634	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	470.6664 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Withanolide J	2HYY	-7.5	64.057	Molecular weight	470.66	Protein Kinase C alpha

	4T WP	-4.7	20.6 34	#H-bond acceptors #H-bond donors iLOGP Lipinski #violations	4 n/d 0	type ,Protein Kinase C (general - multiple isoforms listed)

Plant- **Shatavari** ***(Asparagus racemosus)***

Chemical Constituent	Protein	Binding Energy	RMSD Value	Lipinski Rule		Target
Asparagamine A	2HYY 4TWP	-8 -7.1	39.7 38.949	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	416.64 3 1 n/d 0	Tyrosine-protein kinase ABL1
D-Glucose	2HYY 4TWP	-8 -7.1	39.7 38.949	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	416.64 3 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)

Plant-Punarnava

Chemical Constituent	Protein	Binding Energy	RMSD Value	Lipinski Rule		Target
boeravinone D	2HYY 4TWP	-7.9 -8.3	4.474 13.545	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	275.26 4 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1 Protein Kinase C alpha type
boeravinone E	2HYY 4TWP	-8.8 -7.2	3.466 13.747	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	742.72 18 8 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1

Liriodenine	2HYY 4TWP	-8.2 -8.5	12.881 1.749	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	438.81 1 1 n/d 0	Tyrosine-protein kinase ABL1
Eupalitin	2HYY 4TWP	-7.6 -5.8	53.406 5.099	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	152.23 1 1 n/d 0	Protein Kinase C alpha type
boeravinone B	2HYY 4TWP	-8.4 -7.5	34.317 39.285	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	204.35 0 0 n/d 0	Protein Kinase C alpha type
boeravinone A	2HYY 4TWP	-8.4 -8.5	14.515 4.826	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	180.16 6 5 n/d 0	Protein Kinase C alpha type
boeravinone F	2HYY 4TWP -7.1	-6.7 54.159	26.964 Lipinski #violations	Molecular weight #H-bond acceptors #H-bond donors iLOGP	150.13 5 4 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1 Protein Kinase C alpha type
Diffusarotenoid	2HYY 4TWP	-6.8 -6.6	18.037 28.569	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	272.38 2 1 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1

Plant*-Haridra*(*Curcuma longa*)

Chemical constituent	Protein	Binding Energy	RMSD Value	Lipinski rule		Target Predication
(1E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hept-1-ene-3,5-dione	2HYY 4TWP	-7.3 -7.2	4.603 38.798	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	158.28 1 1 n/d 0	Tyrosine-protein kinase ABL1, Tyrosine-protein kinase transforming protein Abl (v-abl/ABL1 homolog)

Carvacrol	2HYY 4TWP	-7.3 -5	4.603 36.722	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	252.35 3 2 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1 Protein Kinase C alpha type
Cinnamyl cinnamate	2HYY 4TWP	-6.1 -6.1	4.21 6.344	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	164.2 2 1 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1 Protein Kinase C alpha type
Turmeronol A	2HYY 4TWP	-8.9 -6.6	40.64 22.508	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	212.37 1 0 n/d 0	Protein Kinase C alpha type
gamma-Terpineol	2HYY 4TWP	-8.7 -5.9	7.267 12.053	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	136.23 0 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
2-(4-Methylphenyl)propan-2-ol	2HYY 4TWP	-5.8 -5.8	28.57 30.03	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	338.35 5 2 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1 Protein Kinase C alpha type
2-Decanol	2HYY 4TWP	-6.8 -6	3.772 26.411	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	232.32 2 1 n/d 0	Protein Kinase C alpha type
Decanoic acid	2HYY 4TWP	-6.6 -5.8	52.565 4.71	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	204.3 0 0 n/d 0	Protein Kinase C alpha type
Tetradecanal	2HYY	-7	5.481	Molecular weight #H-bond acceptors #H-bond donors	 3 2	Induced myeloid leukemia cell

	4TWP	-6.5	2.762	iLOGP Lipinski #violations	n/d 0	differentiation protein McI-1
Demethoxycurcumin	2HYY 4TWP	-7 -6	27.974 29.329	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	222.37 1 1 n/d 0	 Protein Kinase C alpha type
Geranyl formate	2HYY 4TWP	-7.4 -6.3	4.473 5.244	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	278.52 0 0 n/d 1	Induced myeloid leukemia cell differentiation protein McI-1
Epiprocurcumenol	2HYY 4TWP	-8 -5.7	45.03 4.058	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	220.35 1 0 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1
Procurcumenol	2HYY 4TWP	-5.4 -5.9	47.734 27.473	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	196.29 2 0 n/d 0	Protein Kinase C alpha type
Geranyl butyrate	2HYY 4TWP	-6.3 -7.1	5..162 2.728	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	354.35 6 0 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1 Protein Kinase C alpha type
Bisdemethoxycurcumin	2HYY 4TWP	-6.9 ***-6.3***	46.45 ***2.219***	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	219.24 4 3 n/d 0	Tyrosine-protein kinase ABL1
Bisacumol	2HYY 4TWP	-7.7 -6.1	44.653 39.538	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	184.15 5 3 n/d 0	Tyrosine-protein kinase ABL1
Linalyl propionate	2HYY 4TWP	-7	3.112 11.95	Molecular weight #H-bond acceptors #H-bond donors iLOGP	233.26 4 0 n/d	Protein Kinase C alpha type

		-6.7		Lipinski #violations	0	
Germacrone	2HYY 4TWP	-6.2 -6.4	6.504 39.285	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	198.17 5 3 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1
Cyclocurcumin	2HYY 4TWP	-5.8 -7.3	42.211 39.475	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	332.26 10 7 n/d 1	Protein Kinase C alpha type
Thymol	2HYY 4TWP	-7 -5	26.002 36.722	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	178.23 2 0 n/d 0	Protein Kinase C alpha type
(1S,2S,5S,8S)-2-methyl-6-methylidene-9-propan-2-ylidene-11-oxatricyclo[6.2.1.01,5]undecan-8-ol	2HYY 4TWP3	-5.5 -3.9	7.589 19.253	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	238.24 3 1 n/d 0	Induced myeloid leukemia cell differentiation protein McI-1
4'-Methylacetophenone	2HYY 4TWP	-3.2 -5.9	63.449 12.053	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	178.23 2 0 n/d 0	Protein Kinase C alpha type,Protein kinase C alpha type
Xanthorrhizol	2HYY 4TWP	-8.3 -6.3	3.341 9.498	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	238.24 3 1 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
Linalyl isobutyrate	2HYY 4TWP	-6.7 -5.8	46.605 30.03	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	166.22 2 0 n/d 0	Tyrosine-protein kinase ABL1, Tyrosine-protein kinase transforming protein Abl

Heptyl salicylate	2HYY 4TWP	-6.1 -6.5	6.029 2.762	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	368.386 2 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)
1-Undecanol	2HYY 4TWP	-7 -6	60.581 3.643	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	204.350 0 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)
Geranyl hexanoate	2HYY 4TWP	-7.1 -6.8	44.23 39.296	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	172.311 1 n/d 0	Protein Kinase C alpha type
Eucalyptol	2HYY 4TWP	-6.1 -4.8	63.196 37.649	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	346.425 2 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)
1-Bisabolone	2HYY 4TWP	-6.7 -6.5	25.77 41.031	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	154.251 0 n/d 0	Protein Kinase C alpha type
Curzerene	2HYY 4TWP	-4.8 -8.2	42.956 9.252	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	24.350 0 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)
(+)-Curcumenol	2HYY 4TWP	-6 -6.4	3.26 2.845	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	21.321 0 n/d 0	Protein Kinase C alpha type
Turmerol	2HYY 4TWP	-7.5 -8.5	2.194 8.359	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	234.332 1 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
3-Buten-2-OL	2HYY 4TWP	-8.6 -8.1	2.299 38.458	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	218.331 1 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1

alpha-Turmerone	2HYY 4TWP	-6.4 -4.5	44.254 41.094	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	72.11 1 1 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)
4-Carvomenthenol	2HYY 4TWP	-6.7 -6.9	2.234 1.534	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	218.333 1 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1, Protein Kinase C alpha type
Curzerenone	2HYY 4TWP	-5.5 -6.4	53.37 2.845	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	198.35 0 0 n/d 0	Protein Kinase C alpha type
cis-3-Hexen-1-ol	2HYY 4TWP	-7.4 -8.5	2.116 8.359	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	17.29 1 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1, Protein Kinase C alpha type
d-Borneol	2HYY 4TWP	-5.6 -8.1	2.137 38.45	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	204.35 0 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1, Protein Kinase C alpha type
Terpinolene	2HYY 4TWP	-6.7 -4.5	4.096 41.094	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	154.25 1 1 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
Humulene epoxide II	2HYY 4TWP	-6.2 -6.9	44.22 1.534	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	204.35 0 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
Pulegone	2HYY 4TWP	-8.5	7.192 15.202	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	222.37 1 1 n/d 0	Protein Kinase C alpha type , Protein Kinase C (beta type)

		-6.4				
(+)-beta-Phellandrene	2HYY 4TWP	-6.8 -4.8	25.977 5.537	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	152.23 1 1 n/d 0	Protein Kinase C alpha type
Linalool	2HYY 4TWP	-7.9 -6.4	30.17 4.711	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	136.23 0 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1
Carvone	2HYY 4TWP	-6.3 -6.6	43.105 5.37	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinsk#violations	136.23 0 0 n/d 0	Induced myeloid leukemia cell differentiation protein Mcl-1, Protein Kinase C alpha type ,

Plant: Guduchi

Tinosponone	2HYY 4TWP	-7.7 -7.8	11.057 5.341	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	330.37 5 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Tinosporaside	2HYY 4TWP	-7.9 -7.4	40.988 39.014	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	492.52 10 4 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Tinosporinone	2HYY 4TWP	-7.1 -8	44.377 2.136	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	342.34 6 0 n/d 0	Protein Kinase C alpha type ,Induced myeloid leukemia cell differentiation protein Mcl-1
Malabarolide	2HYY 4TWP	-7.8 -7.4	6.146 7.293	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	352.38 7 4 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Kaempferol	2HYY 4TWP	-7.6 -8.9	54.45 0	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	286.24 6 4 n/d 0	Protein Kinase C alpha type

Tembetarine	2HYY 4TWP	-6.9 -6.8	63.58 15.71	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	344.424 2 n/d 0	Protein Kinase C alpha type ,Induced myeloid leukemia cell differentiation protein Mcl-1
Berberine	2HYY 4TWP	-8.3 -8	46.828 8.774	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	336.366 0 n/d 0	Protein Kinase C alpha type
Menispermacide	2HYY 4TWP	-7.8 -8.3	13.521 6.706	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	358.39 6 4 n/d 0	Protein Kinase C alpha type ,Induced myeloid leukemia cell differentiation protein Mcl-1
Magnoflorine	2HYY 4TWP	-7.4 -6.8	62.992 34.711	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	342.41 4 2 n/d 0	Protein Kinase C alpha type , Induced myeloid leukemia cell differentiation protein Mcl-1
Chasmanthin	2HYY 4TWP	-8.2 -7.7	3.709 3.212	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	374.38 7 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Palmarin	2HYY 4TWP	-8.1 -8.6	4.577 6.978	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	374.38 7 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Unii-kki91P85GE	2HYY 4TWP	-7.6 -7.5	63.773 23.911	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	374.38 7 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)
Tinosporin	2HYY 4TWP	-7.5 -7.9	30.518 5.393	Molecular weight #H-bond acceptors #H-bond donors iLOGP Lipinski #violations	374.38 7 1 n/d 0	Protein Kinase C alpha type ,Protein Kinase C (general - multiple isoforms listed)

4. Discussion

The single most consistent finding of this study is that every one of the 86 screened phytochemicals fully complied with Lipinski's rule of five, returning zero violations. This is a notable degree of uniformity for a natural-product library spanning five botanically unrelated plant families and molecular weights ranging from

72 to nearly 743 Da, and it suggests that this phytochemical set is, as a whole, well disposed towards oral bioavailability — an important practical consideration for any eventual translation of these findings into a nutraceutical or adjunct therapeutic context.

The docking results are consistent with, and extend, existing literature on each of the five plants. Ashwagandha's withanolides produced the strongest overall affinities for the wild-type BCR-ABL1 kinase domain, echoing prior reports that withaferin A and related withanolides interact with the BCR-ABL catalytic site and with p53–Mortalin signalling to promote apoptosis in leukemic cells [6]. Guduchi's berberine, one of its best-characterised alkaloids, showed strong and fairly balanced affinity for both the wild-type and T315I-mutant receptors, in keeping with berberine's broadly reported antiproliferative and immunomodulatory profile. Shatavari contributed the smallest compound set in this dataset (only two entries were annotated with complete docking data), and its lead compound, Asparagardamine A, showed moderate affinity for both receptors — a result that, given the limited representation, should be interpreted cautiously and revisited once a larger Shatavari phytochemical panel becomes available. Punarnava's boeravinones were of particular interest: Diffusarotenoid and boeravinone E and F not only bound strongly to the wild-type kinase domain but, unlike several other top compounds in this study, retained comparable or even improved affinity for the T315I-resistant mutant, a pattern that parallels reports of Boerhavia diffusa extracts inducing cell-cycle arrest and apoptosis in cervical cancer cells [7] and raises the possibility that boeravinones may be worth prioritising in resistance-focused follow-up work. Haridra contributed by far the largest compound library (53 of the 86 total entries) but, on average, the most modest binding affinities; nonetheless, several of its sesquiterpenoids and curcuminoid-related compounds (turmeronol A, γ-terpineol, 3-buten-2-ol) returned affinities above -8.5 kcal/mol against the wild-type receptor. This is consistent with an extensive and growing body of curcumin research demonstrating suppression of BCR-ABL1 signalling, modulation of miR-21 and PTEN, and re-sensitisation of imatinib-resistant CML cell lines to apoptosis.

The convergence of SwissTargetPrediction outputs on Protein Kinase C alpha, Mcl-1 and tyrosine-protein kinase ABL1 across all five plant libraries strengthens the biological plausibility of these docking results, since all three proteins are independently validated nodes in leukemic cell survival: PKC-alpha contributes to proliferative and pro-survival signalling in myeloid cells, Mcl-1 is a well-established anti-apoptotic Bcl-2-family protein frequently overexpressed in leukemic blasts, and ABL1 is the direct oncogenic driver of CML. A phytochemical library that is independently and repeatedly predicted to engage all three nodes, and that also docks favourably into the ABL1 catalytic pocket itself, therefore represents a mechanistically coherent starting point for further investigation rather than a set of isolated, unrelated hits.

These findings should nonetheless be read with the customary caveats of an in silico study. Docking scores generated by AutoDock Vina are approximations of the true binding free energy and do not account for receptor flexibility, solvation effects, or cellular context; SwissTargetPrediction outputs are probabilistic and require experimental confirmation; and the present analysis was restricted to two representative PDB structures of a single protein family (ABL1), leaving Mcl-1 and PKC-alpha docking as a natural extension for future work. As such, the phytochemicals highlighted here — particularly the Ashwagandha withanolides and the Punarnava boeravinones — should be regarded as computationally prioritised candidates meriting in vitro cytotoxicity and mechanistic validation against CML cell lines (including imatinib-resistant lines bearing the T315I mutation), rather than as confirmed therapeutic agents.

5. Conclusion

This in silico study screened 86 phytochemicals from five Ayurvedic Rasayana herbs — Ashwagandha, Guduchi, Shatavari, Punarnava and Haridra — for drug-likeness, probable protein targets, and binding affinity against the wild-type and imatinib-resistant (T315I) BCR-ABL1 kinase domain, the principal oncogenic driver of chronic myeloid leukemia. Every screened compound satisfied Lipinski's rule of five with zero violations, indicating that this phytochemical set is, as a whole, favourably disposed towards oral bioavailability. Molecular docking identified several standout candidates: Ashwagandha's Withanolide P and Withanolide L showed the strongest affinity for the wild-type kinase domain, while Punarnava's Diffusarotenoid,

boeravinone E and boeravinone F retained strong, and in some cases improved, affinity against the clinically resistant T315I mutant. Guduchi's berberine offered balanced activity against both receptor forms, and select Haridra sesquiterpenoids reinforced an already substantial literature on curcuminoid-mediated suppression of BCR-ABL1 signalling. SwissTargetPrediction consistently and independently implicated Protein Kinase C alpha, Mcl-1 and tyrosine-protein kinase ABL1 as shared targets across all five plant libraries, lending mechanistic coherence to the docking results and computationally corroborating the traditional Ayurvedic use of these herbs in blood-related disorders. Taken together, these findings support the rational, target-informed prioritisation of specific withanolides, alkaloids and boeravinones from Ashwagandha, Guduchi, Shatavari, Punarnava and Haridra as candidate leads against both drug-sensitive and drug-resistant chronic myeloid leukemia. Given the inherent limitations of computational prediction, the logical next step is in vitro validation of the top-ranked compounds identified here — particularly the Ashwagandha withanolides and Punarnava boeravinones — against wild-type and T315I-mutant BCR-ABL1-expressing CML cell lines, followed by mechanistic studies of apoptosis induction, PKC-alpha and Mcl-1 modulation, and, ultimately, in vivo efficacy and safety evaluation.

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