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Integrative Management of Acute Promyelocytic Leukaemia: Synergising *Ayurveda* with Modern Oncology – A Narrative Review

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Abstract

Background: Acute Promyelocytic Leukaemia (APL) is a distinct subtype of acute myeloid leukaemia characterised by the chromosomal translocation t (15;17), leading to the formation of the PML-RARA fusion gene that blocks promyelocyte differentiation. The introduction of targeted therapies such as All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO) has dramatically improved survival, transforming APL into one of the most curable haematological malignancies. Nevertheless, treatment-related toxicities, occasional relapse and long-term quality-of-life concerns highlight the need for supportive and integrative therapeutic approaches. **Aim:** To explore the potential role of *Ayurveda* as a supportive integrative approach alongside modern oncology in the management of Acute Promyelocytic Leukaemia. **Methods:** A narrative review of classical *Ayurvedic* texts and contemporary scientific literature was conducted to analyse the conceptual correlation of leukaemia with *Ayurvedic* principles and to evaluate potential supportive therapies. Published studies related to drugs, Samhitas and journals. **Results:** *Ayurveda* describes disease pathogenesis through the imbalance of *Doshas, Dhatus*, and *Srotas*. Conditions such as *Raktaja Vikara* and *Raktarbuda* show conceptual similarities with leukaemia. Several *Ayurvedic* herbs, including *Guduchi* (Tinospora cordifolia), *Ashwagandha* (Withania somnifera), and *Amalaki* (Emblica officinalis), possess immunomodulatory, antioxidant, and adaptogenic properties that may help improve patient resilience, support hematopoiesis, and reduce chemotherapy-related adverse effects. **Conclusion:** Integrating *Ayurvedic* supportive care with modern targeted therapies may enhance patient quality of life and improve tolerance to treatment in APL. However, robust clinical evidence regarding relapse reduction or direct therapeutic efficacy remains limited.

Major Findings: This review highlights that *Ayurvedic* supportive therapies, including Rasayana formulations and immunomodulatory herbs such as *Tinospora cordifolia*, *Withania somnifera*, and *Emblica officinalis*, may help improve immune function, patient resilience, and tolerance to conventional APL treatments. Integrative approaches combining *Ayurveda* with modern targeted therapies have the potential to enhance quality of life; however, stronger clinical evidence is required to validate their efficacy and safety.

Keywords: Acute, M3, Myeloid Leukaemia, Progranulocytic Leukaemia

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1. Introduction

Acute Promyelocytic Leukaemia (APL) is a distinct subtype of Acute Myeloid Leukaemia (AML), characterised by the accumulation of promyelocytes. It is classified under AML due to its rapid progression and the necessity for prompt treatment. The hallmark of APL is the presence of the PML-RARA fusion gene resulting from the t (15;17) chromosomal translocation[1]. This subtype accounts for approximately

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10-15% of AML cases, with an incidence rate of 0.1-0.2 per 100,000 people annually. It predominantly affects adults with a median age of onset in the mid-30s to 40s, although it can occur in all age groups[2]. Over the past few decades, the way Acute Promyelocytic Leukaemia (APL) is treated has exemplified targeted therapy and demonstrated the impact of translational research. APL was initially observed and characterised by Norwegian haematologist LK Hillestad in 1957. Then, in 1959, J. Bernard identified 20 patients with APL, offering a more detailed understanding that included its association with the rapid growth of promyelocytes, severe bleeding episodes, and it's extremely sudden onset[3]. APL represents approximately 10% to 15% of all cases of Acute Myeloid Leukaemia (AML)[4]. APL is classified under the French-American-British (FAB) system as AML-M3. It's marked by a halt in cell differentiation, where leukaemia cells remain stuck at a specific stage of maturation, particularly the promyelocyte stage. In about 95% of cases, there's a distinctive chromosomal translocation between chromosomes 15 and 17 (t (15;17) (q24; q21)), leading to the formation of the Promyelocytic Leukaemia (PML) Retinoic Acid Receptor-Alpha (RARA) fusion protein, commonly referred to as PML-RARA[5]. Leukaemia, which ranks among the leading causes of cancer-related deaths worldwide, is a cancer that impacts the blood and bone marrow, leading to the uncontrolled proliferation of abnormal white blood cells. Clinically, leukaemia manifests in two main forms: (i) acute, which progresses rapidly, encompassing acute lymphocytic leukaemia and acute myelogenous leukaemia, and (ii) chronic, which progresses more slowly, including Chronic Lymphocytic Leukaemia (CLL) and Chronic Myelogenous Leukaemia (CML). Acute Lymphocytic Leukaemia (ALL) stands out as the most prevalent form of cancer in children, constituting about a quarter of all childhood cancer cases and three-fourths of all newly diagnosed leukaemia cases[6]. Childhood ALL occurs at a rate of around 3 to 4 cases per 100,000 children under the age of 15 years. In India, nearly 25,000 children per annum are diagnosed with this cancer[7]. AML makes up roughly 20% of cases of acute leukaemia in children and 80% in adults[8]. As per the latest information available, leukaemia constituted 2.5% of total cancer cases and 3.2% of all cancer-related fatalities, whereas other blood cancers like Hodgkin's lymphoma comprised 0.5% of cancer diagnoses and 0.5% of cancer-related deaths[9]. Global cancer statistics reported approximately 437,033 new cases of leukaemia worldwide, representing about 2.6% of all newly diagnosed cancers[10]. In conventional science, treatment typically involves chemotherapy (anti-cancer drugs), radiation therapy (high-energy radiation to eliminate cancer cells), and bone marrow transplant (replacing blood-forming stem cells after intensive chemotherapy and radiation). Supportive care, like platelet transfusions, helps control bleeding. While conventional medicine effectively targets the signalling pathways driving leukaemia, it can lead to significant side effects by harming healthy cells in the process[11]. APL was previously regarded as one of the deadliest types of leukaemia because of its fast progression, along with a high degree of bleeding complications. The use of targeted therapies such as All-Trans-Retinoic Acid (ATRA) and ATO has changed the way we manage APL from what had been, historically, one of the most fatal forms of leukaemia to now being one of the most treatable forms of hematologic (blood) cancer. Both of these agents work directly on the PML-RARA oncogene, inducing differentiation and apoptosis in the leukemic cells.

2. *Ayurveda* Perspectives

Ayurvedic texts do not explicitly mention leukaemia or its subtypes. Acharya Sushruta, as mentioned in *Nidan Sthana*, explained *rakta arbuda*, and while comparing the signs and symptoms, we can correlate it with leukaemia[12]. However, Acharya Sushruta's description of *Raktaja Arbuda* shows similarities with certain characteristics of lymphocytic and myeloid leukaemias, such as swollen lymph nodes and low platelet counts. Still, the complete pathophysiology of leukaemia, which remains not fully understood even today, cannot be entirely aligned with the *Samprapti* (pathogenesis) of *Raktaja Arbuda* as described by Sushruta. To approximate an *Ayurvedic* understanding, we can attempt to interpret the disease in terms of *Dosha*, *Dhatu*, *Samprapti*, and *Srotas*. This requires translating the concept of hematopoiesis into *Ayurvedic* principles[12]. According to Acharya Charaka, the food we ingest transforms *Jatharagni Paka* (digestive metabolism) into *Anna Rasa* (nutritive essence). This *Anna Rasa* then reaches the *Yakrit* (liver) and *Pliha*

(spleen), where it is acted upon by *Ranjaka Pitta* to produce *Rakta Dhatu* (blood). Therefore, a condition comparable to leukaemia could arise due to impaired formation of *Rasa* dysfunction in *Ranjaka Pitta*, or structural or functional abnormalities in the *Yakrit* (liver) or *Pliha* (spleen)[13].

3. *Ayurvedic* Etiopathogenesis (*Samprapti*)

The intake of causative factors (*nidana sevana*), such as frequent consumption of *Pittala Ahara-Vihara* (pitta-aggravating foods and habits), and an excess of *Amla* (sour) and *Lavana* (salty) tastes, leads to an aggravation of the *Tridoshas*. These aggravated doshas localise in the *Rasa* and *Rakta* dhatus, disturbing their normal functioning. As a result, subsequent dhatus (*Uttarottara Dhatus*) become weakened, eventually manifesting as visible clinical signs and symptoms. If this condition persists, the vitiated *doshas* can spread further throughout the body[14].

Acharya Chakrapani, in his commentary on the *Samprapti* (pathogenesis) of *Pandu Roga*, explains that excessive intake of *Amla*, *Lavana rasa*, and *Pitta-dominant foods* leads to vitiation of *Pitta*. This disturbed *Pitta* causes depletion (*Shoshana*) of the *Rasa Dhatu*, which in turn hampers proper formation of *Rakta Dhatu*, eventually resulting in the clinical features of *Vataja Pandu*[15].

4. Molecular Mechanisms and Targeted Therapies[16]

4.1 PML-RARA Oncoprotein and Targeted Therapy in APL (Acute Promyelocytic Leukaemia)

The PML-RARA fusion protein blocks promyelocyte differentiation, driving APL. ATRA binds RARA to overcome this block, promoting cell maturation. Arsenic Trioxide (ATO) degrades PML-RARA and induces apoptosis. Together, ATRA and ATO synergistically target the oncoprotein, forming the basis of effective APL treatment.

4.2 Emerging Therapies and Future Horizons

Recent research focuses on novel agents and combinations to enhance APL outcomes. Histone deacetylase inhibitors (e.g., vorinostat) and proteasome inhibitors (e.g., bortezomib) show potential in early studies by targeting alternative pathogenic pathways[17]. Immunotherapy approaches, including anti-CD33 monoclonal antibodies and CAR-T cells, are under investigation for their applicability in APL[18]. Additionally, molecular and epigenetic therapies, such as PI3K/Akt/mTOR inhibitors and DNA methyltransferase inhibitors, offer promising strategies to overcome resistance and improve efficacy[19].

4.3 Challenges and Future Directions in APL Management

Resistance to ATRA and ATO remains a concern, with ongoing research aimed at understanding genetic and epigenetic mechanisms to develop targeted solutions[20,21]. **Minimal Residual Disease (MRD)** monitoring through advanced molecular tools like qPCR and NGS aids in early relapse detection and treatment adjustment[22]. However, **global disparities** in access to ATRA and ATO limit treatment equity, emphasising the need for international efforts to improve availability[23]. Continued **innovation** in therapies and strategies is vital to enhance outcomes, reduce side effects, and manage relapses in APL patients[24].

5. Pathophysiology of APL

5.1 Molecular and Genetic Basis

The pathogenesis of APL is primarily driven by the PML-RARA fusion gene resulting from the t (15;17) translocation. This fusion gene encodes an abnormal retinoic acid receptor that disrupts normal myeloid differentiation and leads to the accumulation of promyelocytes[25]. Additional genetic mutations, such as FLT3 and WT1, are often present and can influence disease progression and response to therapy[26]. Understanding these molecular and genetic underpinnings is crucial for developing targeted therapies and personalised treatment strategies.

5.2 Biological Mechanisms

The PML-RARA fusion protein plays a central role in APL by impairing the differentiation of myeloid progenitors and promoting leukemogenesis. It acts by interfering with retinoic acid signaling, which is essential

for the maturation of promyelocytes. This blockage leads to the accumulation of immature cells and contributes to the characteristic features of APL[27]. Additionally, the PML-RARA oncoprotein disrupts the function of PML nuclear bodies, structures involved in various cellular processes, including apoptosis and DNA repair. This disruption further enhances the leukemic phenotype and contributes to the aggressive nature of the disease[28].

6. *Ayurvedic* Treatment Approach

6.1 *Shodhana* (Purification Therapy)[29]

If the patient is eligible, *Shodhana Chikitsa* is administered to eliminate vitiated doshas and toxins:

- *Virechana* (therapeutic purgation) with herbs like *Trivrit* (*Operculina turpethum*) for *Pitta dosha.*
- *Basti* (medicated enemas) to balance *Vata* and support marrow function.
- *Raktamokshana* (bloodletting), although rarely practised in modern settings, is classically indicated in *Rakta Dushti.*

6.2 *Shamana* (Palliative Therapy)[29]

For those unfit for purification, or after detox, herbo-mineral medicines are used to pacify doshas and nourish blood tissue:

- *Hartal-facilitates* the production of new red blood cells, helpful in erythropoiesis and eventually treats severe anaemia. Also act as an immunomodulator.
- *Kumariasava* – blood purifier and immunomodulator.
- *Ashwagandha Churna* (*Withania somnifera*) – *Rasayana*, enhances immunity and reduces fatigue.
- *Guduchi* (*Tinospora cordifolia*) – immune-regulator and adaptogen.
- *Manjistha* (*Rubia cordifolia*) – blood cleanser.

6.3 *Rasayana* Therapy[29]

Rasayanas play a crucial role in restoring the function of *Dhatus* (tissues), especially *Rakta* and *Majja Dhatu* (blood and bone marrow):

- *Chyawanprasha* – generalised immune support.
- *Shatavari* and *Amalaki* – for tissue regeneration and *Pitta* pacification.
- *Pippali Rasayana* – an immune booster with rejuvenating action.
- *Swarna Bhasma* – *Rasayana* with cytoprotective effects.
- *Abhraka Bhasma* – supports hematopoiesis and acts as a *Rasayana.*

7. Current Standard Treatments

Chemotherapy, traditionally using anthracyclines (e.g., daunorubicin, idarubicin) and cytarabine, remains essential but is limited by toxicities like myelosuppression and cardiotoxicity[30,31]. ATRA transformed APL care by promoting differentiation of leukemic cells via PML-RARA targeting, achieving high remission rates, though risks like differentiation syndrome persist[32–34]. ATO induces apoptosis and differentiation by degrading PML-RARA and generating oxidative stress. It is highly effective, particularly in relapsed cases, but demands monitoring for QT prolongation and hepatotoxicity[35–37]. ATRA + ATO combination is now the frontline therapy for low-to-intermediate-risk APL, offering superior remission rates with fewer chemotherapy-related side effects[38–40]. Advances in molecular oncology have enabled the development of targeted and immune-based therapeutic strategies for APL. These emerging treatment approaches, including immunotherapy, epigenetic therapy, and gene-editing technologies, are illustrated in Figure 1.

Advances in APL biology have enabled targeted therapies like FLT3 inhibitors and other pathway-specific agents, offering precision treatment with reduced toxicity[41,42]. Immunotherapy approaches, including monoclonal antibodies and CAR-T cells, aim to enhance immune responses and eradicate minimal residual disease[43–45]. Epigenetic therapies, such as DNA methyltransferase and histone deacetylase inhibitors, can restore normal gene expression and suppress leukemic growth, showing promise in early trials[46,47]. CRISPR/Cas9 gene editing holds potential to correct PML-RARA and other mutations at the genomic level, though it remains experimental and poses challenges like off-target effects[48,49]. Ongoing clinical trials have validated ATRA-ATO as standard therapy and are investigating new combinations with targeted and immune-based agents, reporting improved outcomes[50–52]. Continued drug development focuses on novel compounds targeting specific APL

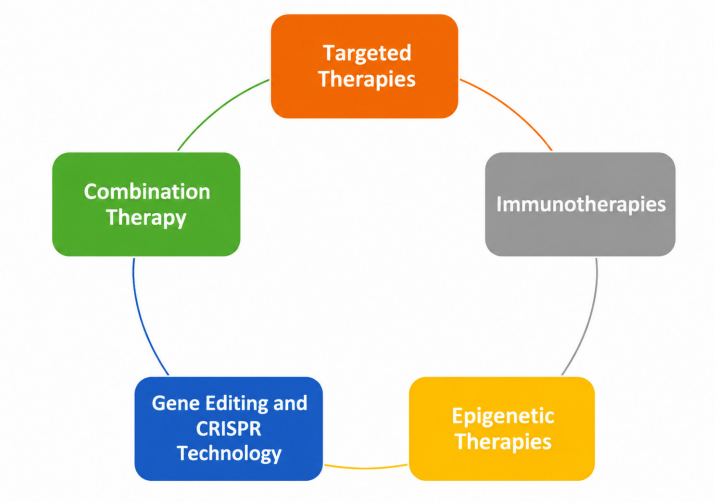


Figure 1. Emerging therapeutic strategies and innovative approaches in the management of Acute Promyelocytic Leukaemia.

mechanisms, crucial for overcoming resistance and enhancing long-term survival[53,54].

8. Patient-Centered Approaches and Quality of Life

Personalised medicine in APL leverages genetic profiling to guide targeted therapy, improving efficacy and reducing toxicity, though challenges like cost and diagnostic access remain[55,56]. Supportive care plays a crucial role in managing side effects, using interventions such as growth factors, antiemetics, and psychological support to enhance quality of life and treatment adherence[57,58]. Long-term survivorship care includes monitoring for late effects like cardiotoxicity and secondary malignancies. Structured follow-up and rehabilitation programs support health maintenance and improve post-treatment outcomes[59,60].

9. Future Directions and Horizons

The use of AI and machine learning in APL is advancing personalised care by predicting treatment responses, relapse risks, and optimising therapy plans through data-driven insights[61,62]. Collaborative research and global initiatives are key to progress, enabling large-scale trials, data sharing, and standardised treatment protocols that expand access to cutting-edge therapies[63,64]. To overcome ongoing challenges like drug resistance and unequal access, research is focused on developing novel therapies and improving global treatment availability, especially in low-resource settings[65].

10. Discussion

Leukaemia is a complex, life-threatening disease that often requires conventional oncological treatments such as chemotherapy, radiotherapy, or bone marrow transplantation. The integration of *Ayurveda* with modern medical science offers a holistic and multidimensional approach to the management of Acute Myeloid Leukaemia (AML). Modern oncology has made significant strides in diagnosis, cytogenetics, targeted therapy, and supportive care, yet the associated adverse effects and disease recurrence continue to challenge clinicians and patients alike. *Ayurveda*, with its deep-rooted understanding of individual constitution (*Prakriti*), *Dosha-Dhatu-Srotas* theory, and *Rasayana* (rejuvenation) therapies, can complement conventional treatments by supporting the body's natural healing mechanisms, improving quality of life, and potentially mitigating treatment-related toxicity[66].

Behind this integrative approach is not to replace, but to enhance. It involves:

- Synergistic healing: Leveraging the curative power of chemotherapy and targeted therapies alongside *Ayurvedic* principles such as *Rakta-Prasadana* (blood purification), *Rasayana* (immune enhancement), and *Agnivardhana* (metabolic restoration), aiming for both disease remission and systemic balance.
- Holistic pathophysiology mapping: While modern medicine identifies AML as a malignancy of myeloid progenitor cells, *Ayurveda* interprets similar symptoms under conditions like *Raktaja Vikara*, *Pandu*, or *Raktarbuda*, involving vitiation of *Pitta* and *Rakta Dhatu*. Understanding these correlations allows for complementary interventions tailored to the patient's *Dosha* imbalance.
- Minimising toxicity and enhancing tolerance: *Ayurvedic* formulations such as *Herbomineral Rasayanas*, *Rakta-stambhaka* herbs, and Immunomodulators may help reduce the side effects of chemotherapy (e.g., mucositis, myelosuppression), improve hematopoiesis, and support faster recovery.

- Personalised treatment approaches: *Ayurveda's* individualised treatment model (based on *Prakriti*, *Vyadhi avastha*, and *Ahar-Vihar*) aligns well with modern precision medicine, potentially offering tailored supportive care regimens to improve outcomes and adherence.
- Mind-body-spirit integration: Incorporating *Ayurvedic* lifestyle practices such as *Dinacharya* (daily regimen), *Sattvic Ahara (pure diet)*, meditation, and *Panchakarma* can help manage stress, improve immunity, and support psycho-oncology goals—areas often overlooked in modern protocols.

Raktashodhaka drugs purify the blood, eliminating toxins and correcting vitiated *Rakta*. *Krimighna* drugs combat internal and external pathogens. *Rasayana* rejuvenates the body, boosts immunity, and delays ageing. *Dhatuposhaka* drugs nourish bodily tissues (*Dhatus*), ensuring strength, vitality, and proper physiological function. Together, these actions support holistic healing and disease resistance in *Ayurveda*[66]. Several *Ayurvedic* herbs possess Raktashodhaka (blood-purifying) properties and may help support haematological balance and immune function. Important examples of these herbs, along with their properties and therapeutic actions, are summarised in Table 1.

Table 1. Important Raktashodhaka Dravyas (blood-purifying herbs) used in *Ayurvedic* management and their pharmacological properties[66]

Dravya (Herb)	Guna (Properties)	Karma (Action)
Manjistha (Rubia cordifolia)	*Guru, Ruksha, Tikta, Kashaya*	*Raktashodhak, Raktastambhak, Varnya*
Neem (Azadirachta indica)	*Tikta, Kashaya, Laghu, Ruksha*	*Raktashodhak, Krimighna, Jantughna, Kushtaghna*
Guduchi (Tinospora cordifolia)	*Tikta, Kashaya, Laghu, Snigdha*	*Raktashodhak, Rasayana, Jwaraghna*
Haridra (Curcuma longa)	*Tikta, Ruksha, Laghu*	*Raktashodhak, Krimighna, Kushthaghna, Lekhana*
Sariva (Hemidesmus indicus)	*Madhura, Tikta, Snigdha, Sheeta*	*Raktaprasadak, Raktashodhak, Tridoshaghna*
Chandan (Santalum album)	*Sheeta, Madhura, Snigdha*	*Raktaprasadak, Daha Shamak, Pittashamak*
Triphala	*Kashaya, Laghu, Ruksha*	*Raktashodhak, Anulomak, Rasayana*
Aloe Vera (Kumari)	*Tikta, Snigdha, Sara*	*Raktashodhak, Virechak, Rasayana*
Patol Patra (Trichosanthes dioica)	*Tikta, Laghu, Ruksha*	*Raktashodhak, Pittashamak, Jwaraghna*

10.1 Suitable Environment for Managing APL

Experts emphasises that APL patients should be managed in specialised centers with rapid genetic diagnostics, ATRA access, full supportive care, and immediate hospitalization during induction, regardless of risk[67]. For non-high-risk patients (WBC $\leq 10\times10^9$/L), ATRA + ATO is now the preferred standard. Phase 3 trials (e.g., GIMEMA, AMLSG, SAL, and NCRI) showed it offers superior or equivalent event-free and overall survival with fewer relapses and reduced supportive care needs compared to ATRA + chemotherapy, despite some reversible side effects[68–71]. For high-risk patients (WBC $>10\times10^9$/L), both ATRA + ATO with cytoreductive chemo and ATRA + chemotherapy are viable, though neither has shown superiority in randomised trials[69]. Anthracycline-based regimens remain effective, and ongoing studies like APOLLO (NCT02688140) aim to determine the best approach[72–76]. Treatment choices should be individualised and include clinical trial options when available.

11. Conclusion

The landscape of APL treatment has undergone transformative changes with the advent of targeted therapies and personalised medicine approaches. ATRA plus ATO has emerged as a preferred regimen for non-high-risk APL, supported by robust clinical evidence demonstrating superior outcomes compared to traditional chemotherapy approaches. Immunotherapies and ongoing research into novel treatment modalities promise further advancements, aiming to enhance therapeutic efficacy, minimise treatment-related complications, and ultimately improve survival rates for patients worldwide. Continued collaboration between clinicians, researchers, and pharmaceutical innovators is essential

to harnessing these advancements and translating them into standard clinical practice for the benefit of APL patients globally.

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Author Contribution

Dr Komal Nandal contributed to the conceptualisation of the study, literature review, and data compilation, and Dr Nilima supervised the work and critically reviewed the manuscript and final approval of the manuscript, while Dr Naveen provided guidance in study design, manuscript revision and drafting of the manuscript. All authors have read and agreed to the published version of the manuscript.

