iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** IV **Month of publication:** April 2025

DOI: https://doi.org/10.22214/ijraset.2025.69260

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue IV Apr 2025- Available at www.ijraset.com

Use of Nutraceutical in Leukemia

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Abstract: ***Leukemia, a heterogeneous group of hematological malignancies, remains a major clinical challenge despite advancements in chemotherapeutic and targeted approaches. Conventional treatments are often associated with significant side effects and drug resistance, necessitating the exploration of alternative or complementary therapies. Nutraceuticals—naturally derived bioactive compounds found in foods and medicinal plants—have gained attention for their potential anti-leukemic properties. These compounds, including curcumin, resveratrol, quercetin, and epigallocatechin gallate, exhibit anti-inflammatory, antioxidant, pro-apoptotic, and anti-proliferative effects through modulation of critical signaling pathways implicated in leukemia pathogenesis. This review provides a comprehensive analysis of various nutraceuticals studied in the context of leukemia, summarizing their mechanisms of action, preclinical and clinical evidence, and therapeutic potential. Additionally, challenges such as bioavailability, safety, and regulatory concerns are discussed, along with future directions including nanocarrier-based delivery and personalized therapy. The integration of nutraceuticals into leukemia management holds promise, but requires further validation through rigorous scientific and clinical research.***

Keywords: Leukemia, Nutraceuticals, Apoptosis, Antioxidants, Phytochemicals, Cancer Therapy

I. INTRODUCTION

A. Overview of Leukemia

Leukemia refers to a diverse group of hematological malignancies characterized by the uncontrolled proliferation of abnormal white blood cells in the bone marrow and peripheral blood. It disrupts the normal production and function of blood cells, leading to anemia, immunodeficiency, and impaired coagulation. Based on the onset and the type of blood cell affected, leukemia is broadly classified into four major types:

- Acute Myeloid Leukemia (AML): A rapidly progressing cancer that originates from myeloid lineage progenitor cells. It is most prevalent in adults and accounts for about 80% of acute leukemia cases in this group.
- Acute Lymphoblastic Leukemia (ALL): Affects lymphoid precursors, primarily in children. It is the most common childhood cancer, though it can occur at any age.
- Chronic Myeloid Leukemia (CML): A slowly progressing cancer of the myeloid line, typically associated with the Philadelphia chromosome (BCR-ABL fusion gene), which drives unregulated cell division.
- Chronic Lymphocytic Leukemia (CLL): Usually diagnosed in older adults, it involves the clonal expansion of dysfunctional B lymphocytes and is often asymptomatic in its early stages.[1]

These subtypes vary in their biological behavior, clinical presentation, treatment approach, and prognosis.

B. Epidemiology and Current Treatment Limitations

Globally, leukemia accounts for over 474,000 new cancer cases and more than 311,000 deaths annually, according to GLOBOCAN 2020 data. The incidence varies by type and region, with higher rates of ALL in children and CLL in older adults, particularly in Western countries. Despite advances in molecular diagnostics and targeted therapies, leukemia continues to pose significant therapeutic challenges. The current standard of care includes chemotherapy, radiation, targeted therapy (e.g., tyrosine kinase inhibitors like imatinib for CML), immunotherapy (e.g., monoclonal antibodies and CAR-T cells), and hematopoietic stem cell transplantation. However, these treatments are often associated with:

- Severe adverse effects such as myelosuppression, organ toxicity, and infections.
- Development of resistance to chemotherapeutic agents or targeted drugs.
- Limited efficacy in relapsed or refractory leukemia.
- High costs and limited accessibility in low- and middle-income countries.

These challenges have prompted the exploration of adjunctive therapies that are safer, cost-effective, and capable of enhancing treatment outcomes.[2]

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C. *Introduction to Nutraceuticals and Their Role in Oncology*

The term "nutraceutical", coined from "nutrition" and "pharmaceutical," refers to food-derived bioactive compounds that provide medical or health benefits, including the prevention and treatment of diseases. Nutraceuticals encompass a wide range of substances, including dietary supplements, functional foods, herbal extracts, vitamins, polyphenols, flavonoids, and fatty acids.

In oncology, nutraceuticals are being increasingly recognized for their multifaceted roles in cancer prevention and therapy. Their mechanisms of action include:

- Antioxidant activity – neutralizing free radicals and reducing oxidative stress
- Anti-inflammatory effects – downregulating pro-inflammatory cytokines
- Apoptosis induction – promoting programmed cell death in cancer cells
- Anti-proliferative effects – inhibiting tumor cell growth
- Modulation of signaling pathways – such as PI3K/AKT, MAPK, NF-κB, and p53

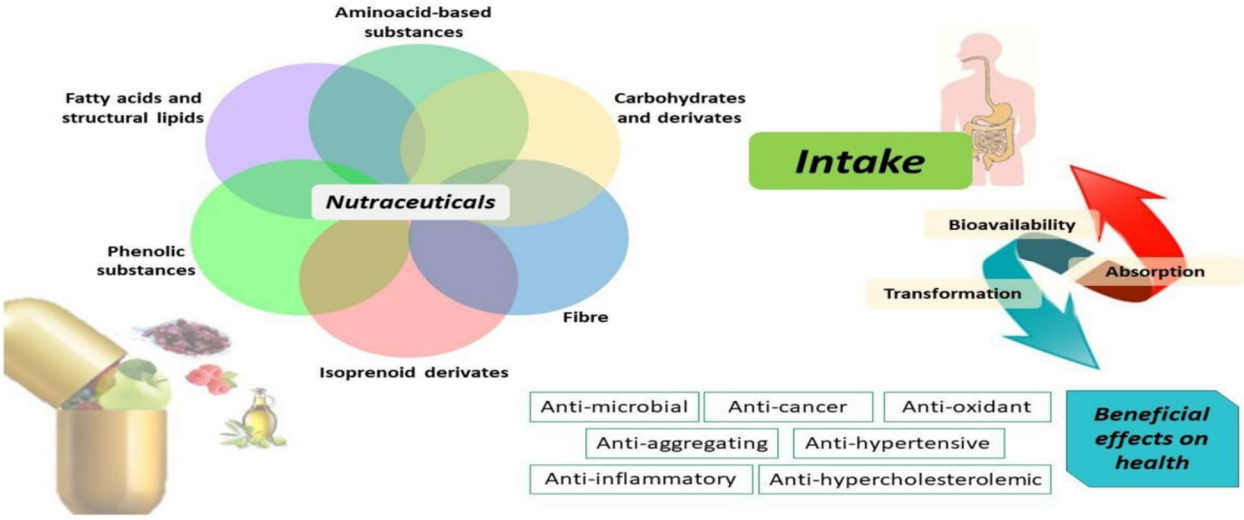
Importantly, many nutraceuticals demonstrate low toxicity, making them attractive candidates for long-term use or combination with conventional chemotherapy to reduce adverse effects and improve efficacy.

In the context of leukemia, numerous plant-derived and dietary compounds have shown promising results in in vitro and in vivo models, with some progressing to early-stage clinical trials. This review explores the potential of these nutraceuticals in targeting key mechanisms of leukemia progression and resistance, highlighting their therapeutic promise and the need for further investigation.[3]

II. OVERVIEW OF NUTRACEUTICALS

A. *Definition and Classification*

The term **nutraceutical** was introduced by Dr. Stephen DeFelice in 1989, combining the words *nutrition* and *pharmaceutical*. It refers to any food-derived substance that provides health benefits, including the prevention and treatment of disease. Unlike pharmaceuticals, nutraceuticals are derived from natural sources and are typically considered safer with fewer side effects.



Classification of Nutraceuticals:

- Dietary Supplements: These include vitamins, minerals, amino acids, enzymes, and other essential nutrients that supplement the diet. Examples: Vitamin D, Omega-3 fatty acids, selenium.
- Functional Foods: Foods that offer health benefits beyond basic nutrition. These are often fortified with bioactive compounds. Examples: Probiotic yogurt, fortified cereals, green tea.
- Herbal Extracts/Phytochemicals: Derived from medicinal plants, these include a vast range of compounds such as polyphenols, flavonoids, alkaloids, and terpenoids. Examples: Curcumin (from turmeric), resveratrol (from grapes), quercetin (from onions), EGCG (from green tea).

These compounds are increasingly being studied for their **chemopreventive and chemotherapeutic** effects in various cancers, including leukemia.[4]

B. Mechanisms of Action Relevant to Cancer

Nutraceuticals exert pleiotropic effects through multiple biochemical and molecular pathways. Their cancer-related benefits include:

- Anti-inflammatory Activity: Chronic inflammation is a hallmark of cancer. Nutraceuticals like curcumin, gingerol, and resveratrol suppress pro-inflammatory cytokines (e.g., TNF-α, IL-6) and inhibit key transcription factors like NF-κB.
- Antioxidant Properties: Oxidative stress contributes to DNA damage and cancer progression. Antioxidant-rich nutraceuticals neutralize reactive oxygen species (ROS) and upregulate cellular antioxidant enzymes (e.g., SOD, catalase).
- Immune Modulation: Certain nutraceuticals enhance immune surveillance by activating natural killer (NK) cells, macrophages, and T cells. They can also modulate cytokine production and antigen presentation.
- Induction of Apoptosis: Apoptosis evasion is a key feature of cancer cells. Nutraceuticals can trigger intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways by modulating pro- and anti-apoptotic proteins (e.g., BAX, BCL-2, caspases).
- Inhibition of Proliferation and Metastasis: By interfering with signaling pathways like PI3K/Akt, MAPK, and Wnt/β-catenin, nutraceuticals slow down cancer cell proliferation, angiogenesis, and metastasis.

These diverse mechanisms make nutraceuticals promising adjuncts in cancer therapy, including leukemia, where multiple signaling abnormalities coexist.

III. PATHOPHYSIOLOGY OF LEUKEMIA & TARGET PATHWAYS

A. Molecular and Cellular Mechanisms in Leukemia

Leukemia is driven by a complex interplay of genetic mutations, chromosomal translocations, epigenetic modifications, and disrupted signaling pathways that lead to impaired differentiation, increased proliferation, and resistance to apoptosis.

Key Molecular Players in Leukemia:

- BCR-ABL Fusion Gene (CML): Resulting from the *Philadelphia chromosome* (t(9;22)(q34;q11)), BCR-ABL encodes a constitutively active tyrosine kinase that drives unchecked proliferation in CML.
- FLT3 Mutations (AML): FLT3-ITD (internal tandem duplication) mutations lead to hyperactive tyrosine kinase signaling, promoting leukemic cell growth and poor prognosis.
- TP53 Mutations: Found in several leukemia subtypes, mutant p53 fails to regulate cell cycle arrest and apoptosis, allowing malignant cells to survive and expand.
- NOTCH1 and JAK-STAT Pathways (ALL): Dysregulation of these pathways is implicated in T-cell and B-cell ALL subtypes, enhancing survival and proliferation.
- Epigenetic Alterations: Aberrant DNA methylation and histone modification contribute to gene silencing and leukemogenesis.
- Apoptotic Dysregulation: Overexpression of anti-apoptotic proteins like BCL-2 and downregulation of pro-apoptotic proteins like BAX are common in leukemia cells.

B. Nutraceutical Modulation of Leukemic Pathways

Several nutraceuticals have been shown to target these dysregulated pathways, offering potential therapeutic benefits:

- Curcumin: Inhibits NF-κB and STAT3, downregulates BCL-2, and upregulates p53 and caspase-3, inducing apoptosis in leukemia cells.
- Resveratrol: Suppresses PI3K/Akt and MAPK pathways, induces S-phase arrest, and triggers intrinsic apoptosis.
- EGCG (Epigallocatechin gallate): Downregulates BCR-ABL expression, inhibits telomerase activity, and reduces oxidative stress in leukemic cells.
- Quercetin: Targets BCL-2 and p53, promotes apoptosis, and inhibits cell cycle progression in CLL and AML models.
- Sulforaphane: Epigenetically reactivates tumor suppressor genes via HDAC inhibition and induces apoptosis through ROS generation.[5]
- Genistein: Inhibits tyrosine kinase activity (similar to imatinib), modulates estrogen receptors, and downregulates oncogenic signaling.

By targeting these molecular abnormalities, nutraceuticals can potentially enhance the effectiveness of conventional therapies, reverse resistance, and offer a lower-toxicity approach for managing leukemia.

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ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue IV Apr 2025- Available at www.ijraset.com

IV. NUTRACEUTICALS WITH EVIDENCE IN LEUKEMIA

This section highlights key nutraceuticals that have demonstrated anti-leukemic potential, based on **preclinical and clinical studies**. These compounds target essential signaling and survival pathways involved in leukemia progression, and may serve as adjuncts or alternatives to conventional therapy.

A. Curcumin

- Source:
  Derived from the rhizome of *Curcuma longa* (turmeric).
- Mechanism of Action:
  - Inhibits NF-κB, thereby reducing inflammatory cytokines and survival signals.
  - Modulates PI3K/Akt, JAK/STAT, and MAPK pathways.
  - Induces apoptosis via mitochondrial pathway (upregulation of BAX, downregulation of BCL-2).
  - Enhances p53 activity and activates caspases.
- Preclinical/Clinical Evidence:
  - In vitro studies show growth inhibition and apoptosis in AML, CML, and ALL cell lines.
  - Curcumin sensitizes leukemic cells to chemotherapy (e.g., doxorubicin, imatinib).
  - Some small clinical trials report improved tolerability and reduced side effects with curcumin supplementation.
- Limitations:
  - Poor oral bioavailability due to low solubility and rapid metabolism.
  - Potential gastrointestinal disturbances at high doses.
  - Requires formulation strategies (e.g., liposomes, nanoparticles) for better delivery.

B. Resveratrol

- Source:
  A polyphenol found in grapes, red wine, peanuts, and berries.
- Mechanism of Action:
  - Induces S-phase cell cycle arrest and apoptosis in leukemic cells.
  - Inhibits Akt and MAPK pathways.
  - Activates caspases and increases ROS levels, leading to mitochondrial-mediated apoptosis.
- Preclinical/Clinical Evidence:
  - Effective against HL-60, K562, and Jurkat cells (AML and ALL models).
  - Resveratrol sensitizes drug-resistant cells to standard chemotherapeutics.
  - Limited clinical data; however, ongoing trials in solid tumors suggest acceptable safety.
- Limitations:
  - Short plasma half-life and limited systemic exposure.
  - Possible drug interactions with anticoagulants and chemotherapeutics.

C. EGCG (Epigallocatechin-3-gallate)

- Source:
  Major catechin found in green tea (Camellia sinensis).
- Mechanism of Action:
  - Inhibits DNA methyltransferases (DNMTs), leading to reactivation of silenced tumor suppressor genes.
  - Suppresses BCR-ABL in CML and inhibits telomerase activity.
  - Induces apoptosis via caspase activation and ROS generation.
- Preclinical/Clinical Evidence:
  - Shown to suppress proliferation in CML, ALL, and HL-60 cells.
  - Some human studies report improved antioxidant capacity and immune modulation.
  - Potential for use in combination therapy with imatinib or dasatinib.

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- Limitations:
  - High doses may cause hepatotoxicity.
  - Limited oral bioavailability, though formulations like EGCG-rich extracts improve efficacy.

D. Quercetin

- Source:
  A flavonoid found in onions, apples, berries, and green leafy vegetables.
- Mechanism of Action:
  - Inhibits tyrosine kinases and downregulates BCL-2 and cyclin D1.
  - Activates caspase-3, leading to apoptosis.
  - Synergizes with chemotherapeutics (e.g., doxorubicin).
- Preclinical/Clinical Evidence:
  - Induces apoptosis in CLL, AML, and CML cell lines.
  - Inhibits leukemic stem cell viability.
  - Some animal models show tumor volume reduction with quercetin-enriched diets.
- Limitations:
  - Potential for estrogenic activity—requires caution in hormone-sensitive cases.
  - Low water solubility and metabolic instability.

E. Sulforaphane

- Source:
  Isothiocyanate found in cruciferous vegetables like broccoli, Brussels sprouts, and kale.
- Mechanism of Action:
  - Acts as a histone deacetylase (HDAC) inhibitor, leading to epigenetic reprogramming.
  - Triggers oxidative stress and induces apoptosis.
  - Inhibits cell proliferation by blocking cyclin D1 and arresting the cell cycle.
- Preclinical/Clinical Evidence:
  - Inhibits proliferation in AML and CML cells.
  - Enhances chemosensitivity to cytarabine and daunorubicin.
  - Studied in clinical trials for solid tumors; limited leukemia-specific trials exist.
- Limitations:
  - Heat-sensitive; cooking reduces activity.
  - Overconsumption may affect thyroid function.

F. Omega-3 Fatty Acids (DHA/EPA)

- Source:
  Found in fatty fish (salmon, sardines), flaxseed oil, and walnuts.
- Mechanism of Action:
  - Anti-inflammatory effects via inhibition of COX-2 and NF-κB.
  - Enhances apoptosis and reduces cell proliferation.
  - Increases chemosensitivity and reduces drug-induced toxicity.
- Preclinical/Clinical Evidence:
  - In vitro studies demonstrate apoptosis induction in leukemic cells.
  - Animal studies show improved survival and reduced leukemic burden.
  - Used in pediatric ALL trials to reduce inflammation and improve treatment tolerance.
- Limitations:
  - High doses may affect bleeding time or interact with anticoagulants.
  - Stability issues—prone to oxidation.

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G. Genistein

- Source:
  A soy isoflavone present in soybeans and soy-based foods.
- Mechanism of Action:
  - Inhibits protein tyrosine kinases, similar to imatinib.
  - Modulates estrogen receptors and downregulates cyclin-dependent kinases.
  - Promotes apoptosis through upregulation of p53 and caspase-3.
- Preclinical/Clinical Evidence:
  - Shown to inhibit growth in CML, AML, and ALL cell lines.
  - Enhances the efficacy of imatinib and cytarabine.
  - Some evidence of bone marrow protection during chemotherapy.
- Limitations:
  - Estrogenic activity could interfere with hormone-sensitive tumors.
  - Controversial effects on thyroid function and reproductive hormones.

H. Garlic-Derived Compounds (Allicin, DADS)

- Source:
  Extracted from Allium sativum (garlic); includes *allicin*, *diallyl disulfide (DADS)*, and *diallyl trisulfide (DATS)*.
- Mechanism of Action:
  - Increases ROS levels, triggering mitochondrial apoptosis.
  - Inhibits cell cycle progression and activates caspases.
  - Downregulates anti-apoptotic proteins and disrupts microtubules.
- Preclinical/Clinical Evidence:
  - Active against AML and ALL cell lines in vitro.
  - Demonstrates selective cytotoxicity toward leukemic cells.
  - Limited clinical data; mostly traditional use and preclinical studies.
- Limitations:
  - Instability of allicin—rapidly degraded during cooking or storage.
  - Gastrointestinal irritation in some individuals.

V. PRECLINICAL AND CLINICAL STUDIES

A. In Vitro and In Vivo Studies

Numerous in vitro studies have demonstrated the anticancer efficacy of nutraceuticals on leukemia cell lines:

- Curcumin induced apoptosis in HL-60 (AML), K562 (CML), and Jurkat (ALL) cells by inhibiting NF-κB and upregulating caspase-3.
- Resveratrol showed potent cytotoxic effects on leukemic stem-like cells, arresting cell cycles and promoting mitochondrial dysfunction.
- EGCG reduced proliferation in CML cells by downregulating BCR-ABL and suppressing telomerase activity.
- Sulforaphane exhibited significant pro-apoptotic activity in AML models, including induction of oxidative stress and HDAC inhibition.
- Garlic-derived compounds such as diallyl trisulfide (DATS) and allicin selectively triggered apoptosis in leukemic blasts without harming normal cells.

In animal models (in vivo), these compounds often show promising results:

- Quercetin reduced tumor burden in xenograft models of AML.
- Omega-3 fatty acids enhanced survival in mice with leukemia via immune modulation.
- Genistein inhibited leukemic proliferation in murine models by interfering with tyrosine kinase signaling.

These preclinical findings collectively highlight the potential of nutraceuticals as anti-leukemic agents, either alone or in combination with existing drugs.[6,7]

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B. Clinical Trials Involving Nutraceuticals

While clinical data is limited, some early-phase trials and observational studies suggest beneficial effects:

- A Phase I trial of curcumin in chronic leukemia patients showed acceptable safety and modest disease control when taken orally over 8 weeks.
- In a pilot study on pediatric ALL, omega-3 supplementation improved patient tolerance to chemotherapy and decreased inflammatory markers.
- Green tea extracts (EGCG) have been tested in early-phase trials in patients with low-risk CLL, demonstrating reductions in lymphocyte counts and lymphadenopathy.
- Resveratrol and genistein are under investigation in broader cancer trials, though leukemia-specific data remains sparse.

Despite promising outcomes, larger randomized controlled trials are urgently needed to confirm clinical efficacy and safety.

C. Synergistic Effects with Chemotherapy

Nutraceuticals often enhance the efficacy of conventional chemotherapeutic agents by:

- Sensitizing leukemia cells to drugs (e.g., curcumin enhances doxorubicin and cytarabine activity).
- Reducing drug resistance through modulation of apoptotic pathways (e.g., quercetin downregulates BCL-2).
- Protecting healthy tissues from chemotherapy-induced toxicity (e.g., omega-3 reduces mucositis and inflammation).
- Improving patient outcomes with adjunctive use (e.g., EGCG with imatinib in CML shows improved tolerability).

These synergistic effects highlight the role of nutraceuticals in combination regimens for leukemia.

VI. CHALLENGES AND LIMITATIONS

A. Bioavailability and Pharmacokinetics

Many nutraceuticals suffer from **poor bioavailability**:

- Curcumin has low water solubility and rapid metabolism.
- Resveratrol and quercetin are quickly degraded and poorly absorbed.
- Strategies like liposomal delivery, nanoparticles, and co-administration with bioenhancers (e.g., piperine) are being explored to overcome these issues.

B. Lack of Standardization and Dosage Guidelines

- Unlike pharmaceuticals, nutraceuticals are not subject to stringent dosage regulations.
- Variability in formulation, extraction methods, and source purity creates inconsistencies in efficacy.
- Standardized dosing and **therapeutic windows** remain undefined for most compounds.

C. Safety Concerns and Drug Interactions

- High doses or long-term use may cause toxicity (e.g., EGCG hepatotoxicity, garlic-induced GI upset).
- Nutraceuticals may interfere with chemotherapy, affecting metabolism (e.g., CYP450 modulation) or potentiating side effects.
- Clinical guidance is necessary to prevent harmful interactions with conventional treatments.

D. Regulatory and Quality Control Issues

- Nutraceuticals often fall under dietary supplement regulations, not pharmaceuticals.
- Lack of FDA or equivalent oversight can lead to contamination, adulteration, and misinformation.
- There is a need for global standardization, quality assurance protocols, and better post-market surveillance.

VII. FUTURE PROSPECTS

A. Nanotechnology in Nutraceutical Delivery

- Nanoformulations (e.g., curcumin nanoparticles, liposomal quercetin) significantly improve bioavailability, stability, and targeting.
- Smart delivery systems enable controlled release and reduced systemic toxicity.
- Ongoing research into nano-nutraceuticals holds promise for leukemia therapy.

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B. Personalized Nutraceutical Therapy

With the rise of pharmacogenomics and precision oncology, there is scope to tailor nutraceutical use based on:

- Genetic polymorphisms
- Disease subtype
- Molecular markers (e.g., BCR-ABL, FLT3 status)

This approach can enhance treatment specificity and patient response.

C. Integration into Mainstream Leukemia Management

Nutraceuticals may soon be included in standard care protocols as supportive agents:

- To reduce side effects
- To enhance treatment efficacy
- To improve patient quality of life

Multidisciplinary collaboration between oncologists, pharmacists, and nutritionists is key to this integration.[8,9]

VIII. CONCLUSION

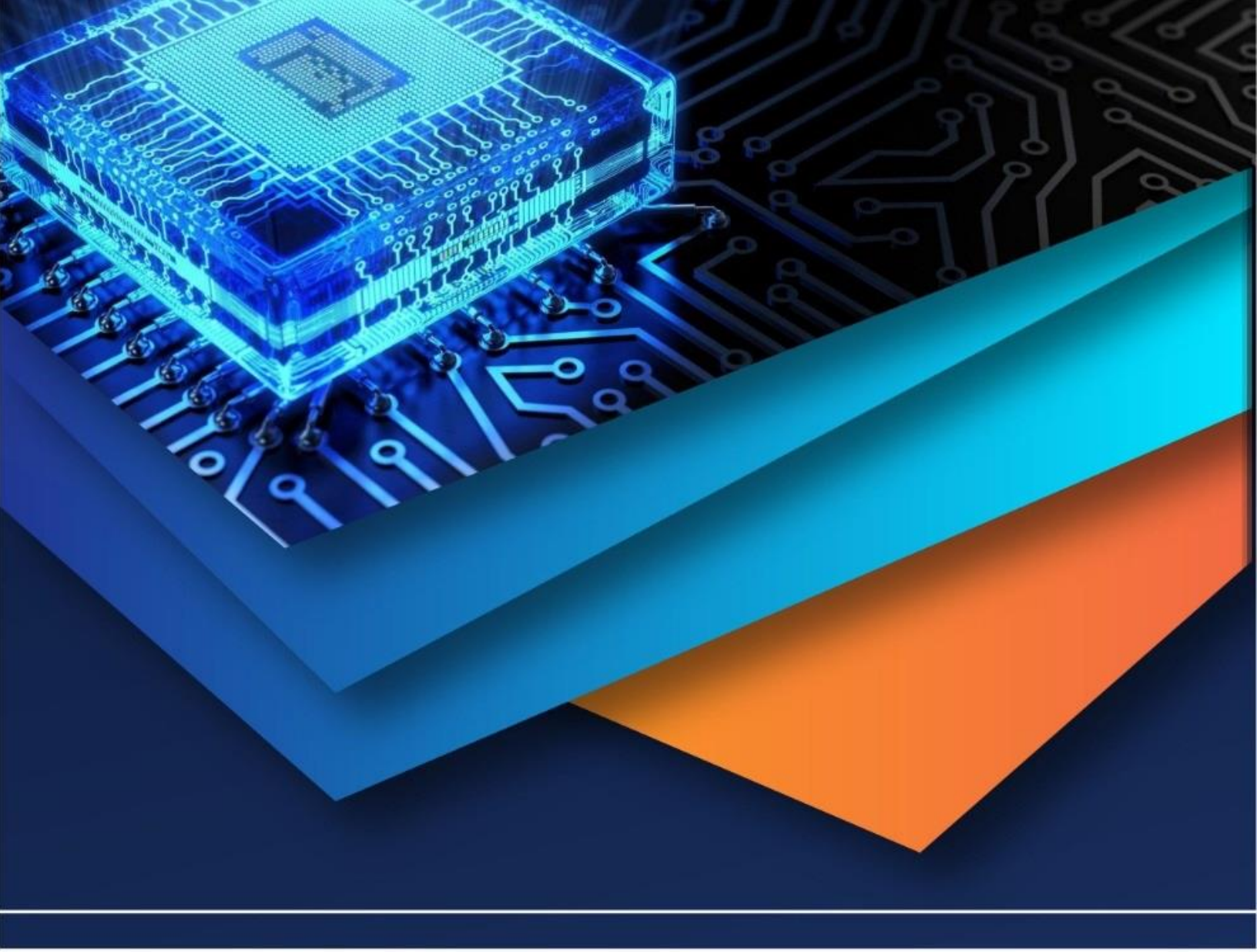
Nutraceuticals offer a novel and promising avenue in the management of leukemia. Through a variety of mechanisms—ranging from epigenetic modulation to apoptotic induction—natural compounds like curcumin, EGCG, and quercetin have demonstrated efficacy in preclinical and early clinical studies.

However, their use is currently limited by poor bioavailability, lack of standardization, and regulatory gaps. While some compounds show synergistic potential with chemotherapy, comprehensive clinical validation is essential before they can be adopted widely. Going forward, advancements in nanotechnology and personalized medicine could revolutionize the role of nutraceuticals in leukemia treatment. A coordinated effort in research, clinical trials, and policy development will be critical to unlocking their full therapeutic potential.[10]

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