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The Combined Supplementary Impact of Ashwagandha, Curcumin, and Green Tea on Hematological Alterations in Benzene-Induced Leukemia in Albino Rats

A Graduation Project Submitted
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In

Biomedical Sciences

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2025

Certification

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The examination committee

Dedication

We would like to thank allah firstly for enabling us in finishing this paper. We dedicate this paper to our parents first for helping us throughout the study time and being supportive both in good and harsh times. Secondly we dedicate this paper to our supervisor (AL.Mohammed.M.Hussien) for his accurate guidance and his support, if not for his supervision we wouldn't be able to finish the project successfully thus, much kind and warm thanks to our supervisor. Lastly we thank Cihan University- Erbil for it is well established facilitates and animal house which we used to carry out our work in.

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Abstract

Objective: Leukemia is characterized by the proliferation of immature white blood cells caused by different factors. Benzene is a chemical solution that can cause leukemia development when exposed to it in a given duration and quantity.

Methodology: In this study, pure benzene was used to induce leukemia in adult male albino rats by intravenous injection of chromasolve benzene solution for 3 weeks every 2 days. Following leukemia induction, rats were divided into 4 groups (6 rats each), and orally treated by gavage with (200mg/kg, 250mg/kg, /200mg/kg) of (ashwagandha, green tea, curcumin) as a combination group which was administrated for daily for 1 Month. Another treatment group was given (300mg/kg) of ashwagandha as a treatment after the treatment period (28 days) rats were cervically dislocated after blood samples were taken by drawing blood directly from the heart. Hematological and histological parameters of (bone marrow- spleen- liver) were carried and evaluated after dissection.

Results: Both treatments increased total WBC counts compared to the negative control group. Although the combination treatment resulted in a slightly higher WBC count, the difference was minor, showing that Ashwagandha alone is also effective in enhancing immune activity. Likewise, RBC counts improved in both treatment groups compared to the control negative group, additionally, both treatments effectively increased red blood cell levels.
According to the previous studies resent of Blast cells indicating for leukemic activity. All treatment groups were shown normal levels of blast cell counts. Combination group—which exhibited the lowest blast cell counts, indicating that combination group was more effective than the ashwagandha-treated group. Histological studies of bone marrow, spleen, and liver have shown tissue structure preserved in the treated group comparing with benzene induced leukemia group. However, the group receiving Ashwagandha supplement shown better tissue structure compared to the combination-treated group.

Conclusion: In summary, ashwagandha has strong anti-leukemic and protective properties against benzene-induced toxicity both individually and in conjunction with curcumin and green tea. Its potential as a synergistic treatment option is suggested by the combination therapy's enhanced therapeutic advantages, which include decreased monocyte levels, increased lymphocyte levels, and greater histological protection in bone marrow, liver and spleen organs.

Keywords: Leukemia, Benzene, Ashwagandha, Curcumin, Green Tea

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List of Abbreviations

Abbreviation	Full Form
AML	Acute Myeloid Leukemia
ALL	Acute Lymphoblastic Leukemia
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
HSCs	Hematopoietic Stem Cells
MSCs	Mesenchymal Stem Cells
MRD	Minimum Residual Disease
EGCG	Epigallocatechin-3-gallate
CYP450	Cytochrome P450
GO	Gemtuzumab Ozogamicin
EGFR	Epidermal Growth Factor Receptor
BM	Bone Marrow
allo-HCT	Allogeneic Hematopoietic Cell Transplantation
FDA	Food and Drug Administration
LSCs	Leukemia Stem Cells
ARA-C	Cytarabine
FLT3	Fms-Like Tyrosine Kinase 3
IDH1/IDH2	Isocitrate Dehydrogenase ½
CR	Complete Remission
TP53	Tumor Protein P53
STAT3	Signal Transducer and Activator of Transcription 3
EGC	Epigallocatechin
EC	Epicatechin
ECG	Epicatechin Gallate
GTE	Green Tea Extract
CGs	Cardiac Glycosides
HMA	Hypomethylating Agents
OS	Oxidative Stress
TGF-β	Transforming Growth Factor Beta
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
JNK	c-Jun N-terminal Kinase
MAPK	Mitogen-Activated Protein Kinase
PI3K/Akt	Phosphatidylinositol 3-Kinase/Protein Kinase B
AML-MSCs	Acute Myeloid Leukemia Mesenchymal Stem Cells
GSTs	Glutathione S-Transferases
NK	Natural Killer
NF2	Nuclear Erythroid 2-Related Factor 2
DR4/DR5	Death Receptor 4/5
cFLIP	Cellular FLICE Inhibitory Protein
Mcl-1	Myeloid Cell Leukemia 1
Bcl	B-Cell Lymphoma-extra Large
XIAP	X-linked Inhibitor of Apoptosis Protein
CDK4	Cyclin-Dependent Kinase 4

GSTT1	Glutathione S-Transferase Theta 1
GSTM1	Glutathione S-Transferase Mu 1
WT1	Wilms Tumor 1
CRSD	Chronic-REM Sleep Deprivation
TLR	Toll-Like Receptors
ABTS	2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)
DPPH	1,1-Diphenyl-2-Picrylhydrazyl
VEGFR	Vascular Endothelial Growth Factor Receptor
BCR	B-Cell Receptor
ALL-MOLZ	Acute Leukemia MOLZ-4 Cells
AML-M4/M5	Acute Myeloid Leukemia - Monocytic/Myelomonocytic Subtypes
HSPCs	Hematopoietic Stem Progenitor Cells
RAS	Rat Sacroma Virus
FAB	French-American-British Classification
EGFR	Epidermal Growth Factor Receptor
MMP	Matrix Metalloproteinase
HNSCC	Head and Neck Squamous Cell Carcinoma
RES	Resveratro
MRP1	Multidrug Resistance Protein 1
MDR1	Multidrug Resistance Gene 1
TP53	Tumor Protein P53
LC	Leukemic Cells
PLT	Platelets
CRP	C-Reactive Protein
BTK	Bruton’s Tyrosine Kinase
CVD	Cardiovascular Disease
TNF-α:	Tumor Necrosis Factor Alpha
IL-6/IL-1β	Interleukin 6 / Interleukin 1 Beta
CD4+	Cluster of Differentiation 4 Positive T Cells
CD8+	Cluster of Differentiation 8 Positive T Cells
CD3+	Cluster of Differentiation 3 Positive T Cells
ROS	Reactive Oxygen Species
NF-kB	Nuclear Factor Kappa-Light- Chain- Enhancer of Activated T Cells
IL-3	Interleukin 3
TLRs	Toll Like Receptors
STAT-1	Signal Transducer and Activator of Transcription 1
HPC	hematopoietic progenitor cell
CEBPA	CCAAT Enhancer Binding Protein Alpha
DDX41	Dead Box Helicase 41
RUNX1	Runt Related Transcription Factor 1
ANKRD26	Ankyrin Repeat Domain 26
ETV6	ETS Variant Transcription factor6
GATA2	GATA Binding Protein 2
MDS	myelodysplastic syndrome
t-MN	Therapy Related Myeloid Neoplasm
sAML	Secondary Acute Myeloid Leukemia
MPN	Myeloproliferative Neoplasm
Bcl-2	B-cell lymphoma 2

AKT	Protein Kinase B
JAK	Janus Kinase
MLL	Mixed Lineage Leukemia
RBC	Red Blood Cells
WBC	White Blood Cells
PLT	Platelets
mols	Malignant Oral Lesions
CYP2E1	Cytochrome P450 2E1
CYP2B	Cythpchome P450 2B
T-reg	Regulatory T Cells
MM	Multiple Myeloma
OEL	Occupational Exposure Limit
ACGIH	American Conference of Governmental Industrial Hygienists
TLV	Threshold Limit Value
PPM	Parts Per Million
IUR	Inhalation Unit Risk
SMR	Standardized Mortality Ratio
NGS	Next Gen Sequencing
SCT	Stem Cell transplantation
CUR	Curcumin
CHD	Coronary Heart Disease
HL-60	Human Promyelocytic Leukemia Cell Line
HPA	hypothalamicpituitary-adrenal
ARE	Ashwagnadha Root Extract
CNS	Central Nervous System
WRE	Witania Somnifera Root Aqueous Extract
THP-1	Human Leukemia Monocytic Cell Line
PUMA	P53 Upregulated Modulator of Apoptosis
WS	Withania Somnifera
WND	Withanolide D
GIT	Gastrointestinal Tract
OS	Oxidative Stress
GSDMD	Gasdermin D
K562	Human leukemia Cell Line K562

CHAPTER ONE

1.0. Introduction

1.1. Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is an aggressive white blood cell cancer that causes symptoms such as organ infiltration and bone marrow failure, it is linked to a comparatively low survival rate. (1).These are primary malignancies of the lymphoid tissues and bone marrow, which are blood-forming organs. A class of hematological cancers originating from blood-forming tissues is known as leukemia. The Greek word "leukos," which means "white blood," is whence the disease gets its name (2). Leukemia is a set of disorders that impact hematopoietic stem cells. They are distinguished by the unchecked growth and accumulation of malignant white blood cells in the bone marrow and peripheral blood (3). Benzene is a common environmental mutagen and significant industrial chemical that is known to cause hematological cancers, including leukemia (4). Benzene and its metabolites can reduce CD4+ T cells, the CD4+/CD8+ ratio, and CD3+ T cells in addition to causing immunological organ atrophy (5). Group 1 carcinogens, including benzene, can cause cancer in both people and animals. In addition to being utilized in numerous sectors, it is found in the environment. Benzene exposure in the public is caused by cigarette smoking, petrol fumes, vehicle exhaust, and benzene-contaminated water and soil (6). In addition to immunological activities, the liver is the first organ implicated in the metabolism of benzene, which is converted to benzene oxide via the cytochrome system, primarily by CYP4502E1. Bone marrow (BM) is the second important organ in the metabolism of benzene (7). Chronic exposure to benzene is associated with a variety of hematological disorders, such as aplastic anemia, myelodysplasia, and leukemia, particularly acute myeloid leukemia (AML)(8).Myeloid cells are more prevalent in the blood and bone marrow in AML patients. The bone marrow produces immature blast cells, which are immature and incapable of providing efficient disease defense (9). The American Cancer Society projects that there will be about 60,650 new cases of leukemia and 24,000 fatalities in the US in 2022, with 20,050 new cases of AML having been reported (10). Currently available treatments for AML involve induction chemotherapy, consolidation with chemotherapy or allogeneic haematopoietic cell transplantation (allo-HCT) and other therapies (11).

1.2. Ashwagandha

Plants are one of the most important sources of medicines in world,Today the large numbers of drugs in use are derived from plants(12).Ashwagandha known as ‘Indian Ginseng’ is one of the important medicinal plant, The phytochemicals from root extracts have antiviral activity and may be effective in controlling the viral infections(13).Additionally, there is evidence to suggest that Ashwagandha supplementation may be helpful in infertility, anticancer and antidiabetic treatment(14). Blood markers were measured over time to help understand the mechanisms of action associated with ashwagandha supplementation (15). Major biochemical elements such as alkaloids and steroids are responsible for Ashwagandha’s therapeutic benefits (16). Phytochemical derived from plant ashwagandha has been receiving great attention due to its anticancer properties

observed in various mice models and tumor cell studies(17).Publications on ashwagandha and its immunomodulatory effect aimed at understanding how ashwagandha affects the immune response and whether it can enhance the body's ability to fight off infections(18). Further, root extracts of ashwagandha displayed anti-leukemic effects on T-lymphoblastoid cell line and induced DNA damage, cell cycle arrest, and enhanced ROS production thus suggesting that ashwagandha exerts its anticancer effects through multiple modes of action.(19).

1.3. Curcumin

Curcumin, the primary constituent of turmeric, is a polyphenol that is produced from the plant Curcuma longa L. and has been utilized in traditional and ayurvedic medicine since ancient times, particularly in China and India. (20). Phytochemicals, such as curcumin—the primary polyphenol found in the rhizomes of (Curcuma longa) are recognized as essential sources for new medications, as they regulate the expression of various oncogenic or tumor suppressor proteins and influence the activity of transcription factors like Forkhead box O, nuclear erythroid 2-related factor 2 (Nrf2), and nuclear factor-κB (NF-κB) in cell signaling pathways..(21)(22).The main issue with curcumin is its limited bioavailability taken orally, caused by inadequate small intestine absorption, rapid metabolism, and rapid systemic clearance. Consequently, several formulations of curcumin have been created. (23). Modern studies confirm the remarkable diversity of curcumin activity, including antioxidant, anti-inflammatory and anticancer properties. The anticancer activity of curcumin has been demonstrated against diverse animal and human cancers, including leukemia (24).Curcumin's anti-inflammatory and anticancer qualities have also been established by other research. IL-6, TLRs, IL-3, and STAT-1 were significantly downregulated after curcumin administration (25).

1.4. Green Tea

Since ancient times, green tea has been a widely consumed beverage. Numerous studies have demonstrated the health advantages of green tea use, including the prevention of cancer and the treatment of infectious disorders (26). Tea can be divided into numerous categories based on the various ways that different nations define it. The tea is classified into six main lines based on the level of fermentation: green tea, black tea, white tea, yellow tea, oolong tea, and dark tea (27). It is made up of catechins, the most notable of which are epicatechin (EC), epigallo-catechin (EGC), epicatechin-3-gallate (EGG), and epigallocatechin-3-gallate (EGCG). (28).EGG has drawn growing attention, especially for AML therapy, due to its capacity to selectively trigger leukemic blasts rather than normal blood cells to undergo apoptosis (29).The primary benefit of antioxidants is their ability to reduce the risk of several cancer types. Green tea lowers the risk of thyroid, colon, stomach, esophageal, prostate, and breast cancers. This has been both approved and demonstrated (30). Because of these advantages, there has been debate about suggested green tea consumption and dietary guidelines (31). This property is shared by all green tea

catechins (also known as polyphenols), and it is used to treat many malignancies in vivo or in vitro, such as myeloidasa and lymphoid leukemia. The effect of these polyphenols is a morphological change that is dose- and/or time-dependent (32).

1.5. AML Treatment Limitations

AML has several subtypes with varying prognostic characteristics, these subtypes can be efficiently treated with targeted and selective treatments, which are still undergoing optimization (33). Treatment for AML is still problematic for high-risk patients who are not eligible for intensive care or allogeneic hematopoietic stem cell transplantation (alloHSCT), which has a poor prognosis (34). Until recently, the majority of patients received similar chemotherapy treatments however, as a result of the identification of genetic anomalies, AML therapy choices have increased (35). Significant progress has been made in AML pathophysiology and therapeutic vulnerabilities yet, despite these developments, certain subtypes, such as TP53 mutations, continue to have poor prognoses (36). Normal (HSCs) undergo molecular alterations due to AML thus, forming immature cells that multiply in the bone marrow, generating non-functional cells that replace and compete with normal hematopoietic precursors known as blasts (37). The aim of leukemia induction treatment is to attain total remission (CR), ideally with no detectable remaining illness (MRD)(38). Leukemia stem cells (LSCs), which derive from HSCs and have the capacity for endless self-renewal, are the primary cause of leukemogenesis and treatment resistance.(39). It is believed that (LSCs) are abundant in chemo resistant AML cells, and those intrinsic variables such as growth factor signaling, epigenetic regulation, metabolic reprogramming, and bone marrow microenvironment control these cells (40).According to established views, existing chemotherapy medications could only largely destroy AML blast cells—not LSCs (41). One of the main issues is refractory disease after remission which has been linked to therapy-resistant leukemia cells, also known as minimum residual disease (MRD), which contains LSCs (42). Primary refractory illness is defined by the European LeukemiaNet as failing to achieve complete remission (CR) following two courses of rigorous induction treatment (43). Additionally Managing AML is more difficult in lower-middle-income nations because of higher infection rates, delayed diagnosis, unavailability of newly targeted medicines, and mostly financial restraints cause of high cost of treatment (44). Treatment effectiveness is severely restricted by the development of primary and secondary resistance mechanisms, Understanding these pathways is essential to create novel therapeutic strategies against AML (45). Plants have garnered more attention in recent years as potential treatments for serious human illnesses including cancer (46). Novel chemo preventive therapies are needed to enhance the effectiveness of established cancer therapies similarly; phytochemicals are a major source of novel medications for the treatment of cancer (47). Recent studies have revealed that natural compounds including ashwagandha, green tea, and curcumin are potential chemo preventive and chemotherapeutic agents (48).

Aim of Current Study

The study aimed to study and explore the therapeutic effects of ashwagandha supplement solely and as a combination with curcumin and green tea supplements on hematological parameters on benzene- induced leukemia on male albino rats.

CHAPTER TWO

2.0 Literature Review

2.1. Leukemia

A kind of hematological cancer called leukemia is brought on by aberrant white blood cells and a decrease in the bone marrow cells' capacity to make platelets and red blood cells. It accounts for over 40% of all malignancies in children and young people under the age of 20, making it the most common cause of cancer in this age range. Leukemia makes for 1.2% of all malignancies in adults. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, the incidence of leukemia rose by 19% worldwide between 2007 and 2017 (49) .Leukemia frequently starts after hematopoietic stem cell lineage dysfunctions. Early leukemia identification for efficient treatment is one of the most crucial topics in the field. As a result, acute leukemia is regarded as a diverse subset of hematopoietic progenitor cell (HPC) malignant diseases, exhibiting a range of clinical features, inconsistent response to existing treatments, and molecular genetic abnormalities. Acute leukemia often strikes youngsters between the ages of two and three, and it generally appears suddenly. Conversely, the majority of individuals with chronic leukemia are elderly. Blood tests, cytogenetic techniques, and bone marrow examination are frequently used in conventional leukemia detection procedures. However, there are many drawbacks to these conventional methods, including the need for unfeasible testing apparatus and difficulties with the clinical procedure (50). The following are risk factors for leukemia: chemotherapy, radiation (therapeutic, occupational, and battlefield), genetic disorders and anomalies, family history, chemical exposures (such as those at work and home), and lifestyle elements such as smoking. While certain exposures have been linked to certain leukemias, the most significant risk factors affect several subtypes. For instance, inhabitants of Japan who received significant amounts of ionizing atomic bomb radiation have been linked to higher death rates from ALL, AML, and CML, three non-CLL leukemias separately. There are probably similarities in the ways that risk factors common to leukemias facilitate carcinogenic processes (51).

2.1.1. Leukemia Types

The main subtypes include acute myeloid leukemia (AML) and chronic myeloid leukemia (CML)**,** which affect the myeloid lineage, and acute lymphoblastic leukemia

(ALL) and chronic lymphocytic leukemia (CLL), which involve the lymphoid lineage (52).

2.1.1.1Acute myeloid leukemia (AML)

AML is a diverse group of leukemias arising from the clonal transformation of hematopoietic precursors through chromosomal rearrangements and multiple gene mutations. Over the past three decades, collaborative clinical research by pediatric cancer groups worldwide has led to significant improvements in disease-free survival. Future advancements in treating AML in children are likely to stem from a deeper understanding of its biology and the development of new molecularly targeted therapies to complement traditional chemotherapy.(53)Syndromes of familial predisposition That families occur in which many individuals (in both childhood and adulthood) are afflicted by a myeloid malignancy has been long acknowledged. Certain genotypes linked to heritable haematologic cancers have been identified in recent decades. Isolated abnormalities (CEBPA, DDX41) or those associated with other abnormalities (either a platelet disorder or organ dysfunction), such as RUNX1, ANKRD26, ETV6, GATA2, Li Fraumeni syndrome (TP53), and bone marrow failure syndromes (Fanconi anemia, dyskeratosis congenita), are among the several categories for myeloid neoplasms with germline predispositions that are included in the most recent WHO classification (54). (AML) may develop from scratch or as a side effect of an existing cancer. Secondary leukemia can be divided into two main categories: therapy-related myeloid neoplasm (t-MN), which develops as a side effect of previous cytotoxic therapy, and AML resulting from an antecedent myeloid malignancy—myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or MDS/MPN overlap syndrome, where progression to AML is thought to be a normal part of the disease's natural course (secondary AML (sAML) (55).

2.1.1.2 Chronic myeloid leukemia (CML)

CML is a hematopoietic disorder characterized by the malignant proliferation of bone marrow stem cells. Its defining cytogenetic feature is the Philadelphia (Ph) chromosome, a reciprocal t (9;22)(q34;q11) translocation that results in a large 9q+ and a small 22q– chromosome.(56) With an annual incidence of 1.0–1.5/105, (CML) is an uncommon hematologic cancer that does not significantly differ in incidence by race or geography. The frequency of CML is expected to increase from 70,000 in 2010 to 180,000 in 2050, making it the most common myeloid neoplasm in the United States. The only known risk factor for CML development is ionizing radiation (57). Since rituximab, an anti-CD20 antibody was licensed in 2010 for the treatment of CLL, the indications for therapy have altered significantly, and it is now suggested in both symptomatic and advanced stages. Chemotherapy medications have been the mainstay of treatment until then (58).

2.1.1.3. Chronic lymphocytic leukemia (CLL)

CLL is an age-adjusted incidence rate of 6 cases per 100,000 individuals. The disease is driven by two primary pathological mechanisms: increased cell proliferation through B-cell receptor (BCR) signaling and resistance to programmed cell death due to the overexpression of B-cell lymphoma 2 (Bcl-2). These processes result in the accumulation of CLL cells, leading to tissue infiltration and impaired immune function. Bruton’s tyrosine kinase (BTK) plays a crucial role in mediating BCR signaling (59). Because of innate immunological deficiencies associated with their original disease and as a result of treatment, individuals with chronic lymphocytic leukemia (CLL) are often more likely to get bacterial and viral infections. Immunodeficiency in CLL is caused by a number of pathways, including aberrant

humoral and cellular immune responses brought on by both quantitative and qualitative flaws in immune effector cells, which may also lessen vaccination response (60).

2.1.1.4. Acute lymphoid leukemia (ALL)

ALL is a hematological neoplasm that impacts precursor cells of the B, T, and NK lineages, with a higher prevalence in children. The pathophysiology of ALL involves chromosomal abnormalities and genetic mutations that disrupt the differentiation and proliferation of lymphoid precursor cells. Although research is limited, leukemogenesis is thought to result from a complex interplay of genetic and environmental factors that drive cellular changes. While environmental factors have been investigated as potential contributors to ALL development, the global literature presents conflicting findings. This review aims to explore the key exogenous factors associated with ALL (61).

2.2. Epidemiology of Leukemia

Age and race significantly influence the prevalence of leukemia. In the United Kingdom, 42.8% of all leukemia cases are found in individuals aged 65 and older. Similarly, a study conducted in the United States reveals that age-adjusted leukemia incidence rates are highest among the White population at 15 per 100,000, followed by 11 per 100,000 for Blacks, and 10.6 per 100,000 for Hispanics. Although leukemia occurs across all age groups, its occurrence differs depending on the specific type of the disease (62). Significant progress in understanding the pathophysiology and improving treatment for acute myeloid leukemia (AML) is happening rapidly. The discovery of cytarabine (ara-C) and anthracyclines in the 1970s led to the development of the "3+7 regimen" (3) days of daunorubicin and 7 days of cytarabine), which became the standard treatment. This approach has achieved long-term cure rates of 30–40% in younger AML patients. Early studies focused on patients aged up to 50–55 years, showing 5-year survival rates of 40–45%. Later studies, included patients up to 60 years old, reported slightly lower 5-year survival rates of 30–35%. In older patients (60 years and above), these intensive chemotherapy regimens yielded lower 5-year survival rates, typically below 10 15% (63).

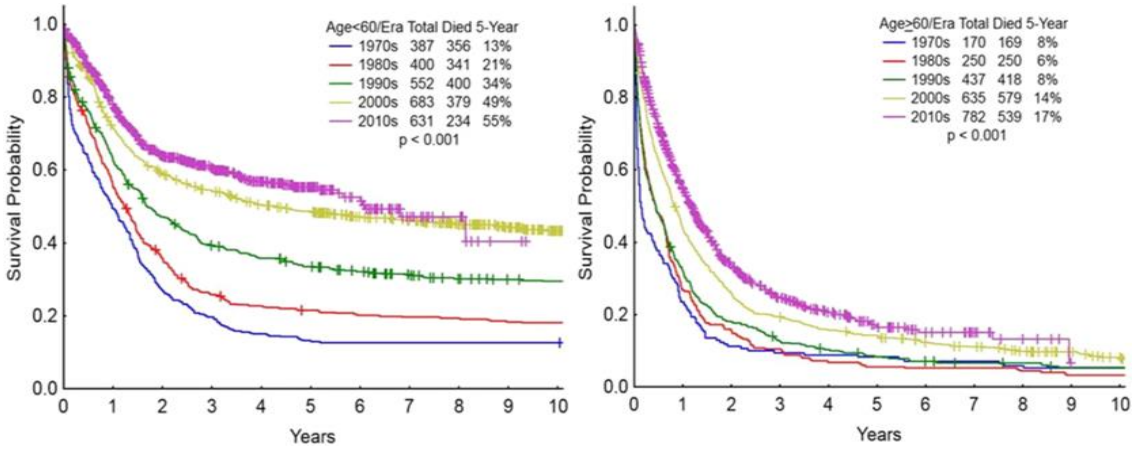

Figure 2.1 Age and Treatment Era-Based Survival of De Novo Acute Myeloid Leukemia at MD Anderson (1970–2017): Panel on the left: age under 60; panel on the right: age above 60 (63).

2.3. Pathophysiology

Mutations that could lead to the abnormal maturation of healthy bone marrow cells or proliferative growth of immature cells results in AML. Research from the Cancer Genome Atlas Research Network has demonstrated that AML arises from a founding

clone and at least one subclone, and mutations in epigenetic regulation, such as in IDH1 or IDH2, occur early in AML evolution. Multiple different mutations that are thought to play a role in the development of AML have been identified and include those that affect tumor suppressor genes, chromatin modification, RNA processing, and chromosome segregation. For example, mutations in signaling proteins such as FLT3 promote proliferation through the RAS/JAK/AKT signaling pathway and IDH mutations affect DNA methylation (64). Hyper leukocytosis has historically been associated with specific cytogenetic and molecular features. Risk factors include FLT3-ITD mutations, abnormalities involving the MLL gene on 11q23, and the monocytic and myelomonocytic subtypes of AML (FAB classifications AML M4 and M5). However, the molecular mechanisms driving hyperleukocytosis remain poorly understood. Over the past two decades, research has shed light on the role of adhesion molecules and cytokines in leukostasis formation and hematopoietic stem cell (HSC) homing to the bone marrow. Endothelial selectins have been identified as key mediators in leukemic blast adhesion to the vascular endothelium, playing a critical role in the development of leukostasis (65).

2.4. Manifestation and Symptoms

Few studies have recently documented oral manifestations as the initial clinical indicators of leukemia since these symptoms are often stated in clinical case reports that differ depending on the leukemia type and individual.® In order to guide the diagnosis of leukemia by clinical indicators in the mouth as part of the initial clinical manifestations of the disease, this integrated study sought to determine which oral tissues displayed the first MOLs (66). Up to 50% of individuals with leukemia have been reported to have clinically noticeable ocular involvement at the time of diagnosis. Haematological abnormalities like cytopenia and leukocytosis, as well as secondary to chemotherapy or immunosuppression, can cause indirect ophthalmological manifestations, or direct leukemic infiltration of various ocular tissues, including the optic nerve, choroid, retina, iris, ciliary body, and anterior chamber (67). Leukemia can present orally in 56% of patients with petechiae or spontaneous bleeding, 53% with mucosal ulceration, and 36% with gingival expansion, with or without necrosis. These characteristics are the most typical early signs of leukemia. Along with mucosal pallor, there may also be increased caries prevalence, candidiasis and herpes opportunistic infections, temporomandibular joint arthritis, and osteolytic lesions in the jaw. Less often mentioned were other oral symptoms as palatal pigmentation, tooth discomfort and movement, tongue hemorrhagic bullae, cracked lips, parotid edema, and chin numbness. All of these oro-dental characteristics, in Figures 1 and 2, demonstrate typical oro-dental symptoms in individuals with AML (68).

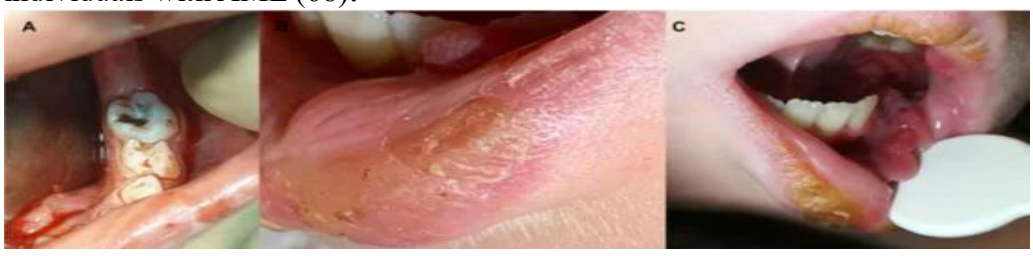

Figure2.2 (A)caries in the lower primary molars, intraoral bleeding, and gingival enlargement/hyperplasia. (B) Cracked lips and gingival enlargement. (C) Cracked lips, gingival enlargement/hyperplasia, and buccal bleeding (68).

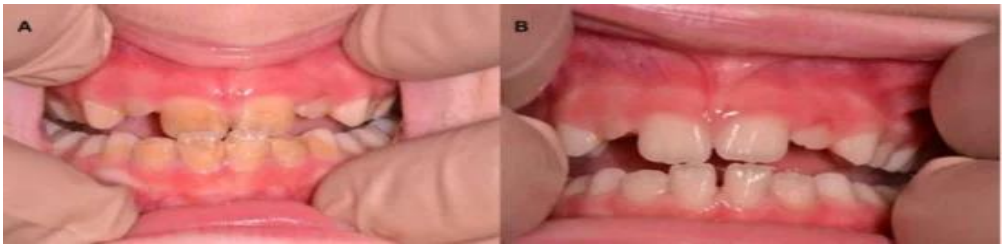

Figure 2.3 (A) Calculus stone and enamel discolouration. (B) The intraoral image of the patient is depicted in Figure 2A following a few scale and polishing treatments that removed the calculus stone and discoloration (68).

2.5. Risk adapted therapy

A sophisticated treatment algorithm that incorporates the patient's objectives of care, comorbidities, and disease features, including the particular mutational profile of their AML, is necessary due to the intricacy of the diagnostic and therapeutic processes as well as the availability of recently authorized drugs. Our proposed framework is only the start of the conversation (69). Genetic factors showed higher chances of developing leukemia and has been associated with specific genetic abnormalities, like chromosomal mutations as well as genetic syndromes. Li-Fraumeni syndrome, Down syndrome, and some hereditary bone marrow failure diseases are a few examples. Exposure to Ionizing radiation: Leukemia risk can be increased by high levels of ionizing radiation, like those received during nuclear accidents or some cancer treatments. Chemical exposures: Long-term exposure to some chemicals, like formaldehyde and benzene, has been connected to a higher risk of leukemia. These substances are employed in a few specific industries, including rubber manufacturing, petroleum refining, and some chemicals production. Smoking cigarettes has been associated with an increased risk of acute lymphoblastic leukemia as well as acute myeloid leukemia, especially in adults (70).

2.6. Benzene

The International Agency for Research on Cancer determined that benzene is carcinogenic and provided evidence of its carcinogenicity in both occupational and non-occupational situations. If either occupational or non-professional exposure occurs, benzene is mostly absorbed by inhalation. It is principally degraded in the liver through processes that are catalyzed by two isoforms of cytochrome P450 (CYP) oxidase, 2E1 and 2B resulting in benzene oxide. (71). additionally, they have the ability to trigger the generation of reactive oxygen species (ROS), damage DNA, and induce mutations. Workers in a variety of sectors, including printing, painting, shoe manufacture, rubber, petroleum, and others, are frequently exposed to benzene, a common industrial chemical (72). The spontaneous rearrangement of benzene oxide to phenol produces hydroquinone and/or catechol metabolites, which can both be further transformed into hazardous metabolites. ROS are produced when certain metabolites build up in the bone marrow, activating phenolic metabolites to

semiquinone radicals, these radicals cause oxidative damage to different stem and progenitor cells as well as bone marrow niches (73). Many blood disorders can arise from the hematotoxic effects of benzene on bone marrow. Benzene and its metabolites target the bone marrow, causing thrombocytopenia, pancytopenia, aplastic anemia, progressive leukocytopenia, hypercellular bone marrow, and decreased neutrophil and absolute lymphocyte counts. Even modest levels of benzene exposure (e.g., 10 ppm) are linked to bone marrow dysfunction and changes in blood cell count (RBC-WBC-PLT) counts in comparison to controls, but high levels of exposure depress peripheral blood cell counts (74). The symptoms of chronic poisoning from benzene exposure include headaches, lightheadedness, nausea, vomiting, trouble focusing, and anemia, which frequently include mucosal and subcutaneous bleeding. The systemic effects of benzene lead to diseases in the neurological, gastrointestinal, liver, renal, cardiovascular, respiratory, endocrine, and reproductive systems, as well as dermatological, local impacts, hematological, immunological, and allergy systems (75). Benzene exposure at work has mostly been linked to higher rates of blood illnesses, including non-Hodgkin's lymphomas, chronic myeloid and acute lymphoid leukemia, leukemia, lymphoma, and myelodysplastic syndrome (76) Benzene's airborne lifespan varies from a few hours to many days, based on the surrounding environment and the existence of other contaminants. The primary way that benzene degrades in the environment is by being oxidized by hydroxyl radicals and then being removed by rain. Consequently, the link between exposure to benzene and several hematological malignancies has been recently shown by a number of meta-analyses (77).

2.6.1. Relation of Benzene with Thrombocytopenia

There is a notable dose-response link between bone marrow depression, such as leucopenia or thrombocytopenia, and the initial stage of benzene-induced hemotoxic lesion. (78). A study (79) examined the effects of benzene inhalation (50 ppm, 6 h/day, 5 days/week, 6 weeks) by Benzene inhalation, 24 mice /group-of eight weeks of age, the study showed that inhaled benzene exposure augments platelet-leukocyte aggregate formation by 3-fold. This was accompanied by 1.6-fold increase in circulating levels of platelet microparticles in benzene-exposed mice. Together these data suggest that benzene exposure enhances platelet activation and platelet-derived micro particles. A 16-month research (80) on shoe producers exposed to benzene revealed that exposure to benzene at levels below 1 ppm might nonetheless harm the human body and hematological system. During the duration of one month (monitoring period). Leukocyte and platelet counts were considerably lower in the lowest exposure group compared to the control values (8–15% lower), according to the individuals' hematological assessments. The decrement was greater in the highest exposure group. In a study done in china (81) on benzene toxicity, blood samples were taken from ten healthy individuals and ten patients who had been exposed to benzene over an extended period of time in order to examine their blood characteristics. It indicated thrombocytopenia in the study group, with the chronic exposure group showing a drop of (95.80 ± 26.92) and the control group showing a decrease of (261.40 ± 63.53).

2.6.2. Relation of Benzene with Leukopenia

According to a number of studies, persons who are exposed to benzene on a long-term basis had lower levels of WBC, RBC, PLT, and total neutrophils, among other blood parameters. According to other research, benzene exposure can damage certain immunoglobulin levels in both humans and animals and cause immunosuppression by lowering T-reg cells, NK cells, and B and T lymphocytes (82). In a trial (83) five animals per sex per treatment group received oral benzene at dosages of 0, 300, and 1000 mg/kg bw per day. According to the data, relative monocyte counts dramatically increased while total white blood cell (WBC), absolute lymphocyte, and absolute eosinophil cell counts significantly dropped. In 2020, a study (84) was carried out in Basra City that examined 72 men who had been exposed to benzene for at least five years in various benzene stations. WBC counts for the exposed group and non-exposed group decreased significantly (4198.4 ± 337.5 vs. 6478.1 ± 381.4), respectively. In comparison to the control group, there was a decline in all evaluated WBC types (lymphocytes, monocytes, and neutrophils). In a study (85) conducted in Nigeria, 48 female rats from 8 groups—6 of which received a dosage of 200 mg/kg of benzene—were examined to determine the impact of extra-virgin olive oil on benzene haematotoxicity. The WBC count decreased in the benzene-treated group (3.700±0.4219) and in the control group (5.550±0.2306).

2.6.3. Relation of Benzene with Cancers

Immunosuppression and persistent inflammation are two important characteristics of carcinogens in which the immune system is involved. The U.S. Environmental Protection Agency has categorized benzene as a category A (known human carcinogen) (86). Benzene exposure can cause genotoxicity even at exposure concentrations below 3.25 mg/m3. Genotoxicity could be a potential carcinogenic mechanism behind the cancerous impact of benzene. According to epidemiological research, benzene exposure is linked to genetic damage. Additionally, several studies have found that workers exposed to benzene had higher rates of chromosome aberrations (CA), micronucleus (MN), and sister chromatid exchange (SCE) (87). The number of mutations needed for cell transformation has been unclear, despite the fact that cancer has been linked to the accumulation of mutations in tumor suppressor and oncogene genes. A previous study discovered that only three driver gene mutations are needed for the development of lung and colorectal cancers which is fewer than the number expected to form cancers (88). Prior research has demonstrated that exposure to benzene is associated with teratogenic effects and may raise the risk of breast cancer through mutations. In the mammary gland, benzene and its metabolites may cause dysplasia and neoplastic transformation by altering the endocrine system (89). Adults who are exposed to benzene are known to develop acute myeloid leukemia. Studies linking benzene to a number of severe health issues, including blood-related conditions and an elevated risk of leukemia, have been verified (90).

2.6.4. Relation of Benzene with Leukemia

Benzene can cause AML and may raise the risk of multiple myeloma (MM), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL).China has established the occupational exposure limit (OEL) for benzene at 3 mg/m3 (0.92 ppm), while the US ACGIH has reduced the TLV to 0.02 ppm. Workers who are exposed to less than 1 ppm of benzene may yet suffer adverse health effects, according to reports. Similarly, a research found that cumulative benzene exposures much below 1 ppm-year were associated with an 11-fold incidence of AML (91).A study of 150 benzene-exposed workers—82 men (54.67%) and 68 women (45.33%)—who did not smoke was carried out in the city of Khon Kaen, Thailand (92) The research comprised 98 petrol stations, with some workers being fueling employees, rather than cashiers. Lifetime cancer risk was found to be between (1.4×10^{-5} and 8×10^{-5}) which resulted in an unacceptable, life time risk as determined by the IUR ($>2.2 \times 10^{-6}$). Furthermore, fueling workers' average lifetime cancer risk from benzene exposure ($>2.2 \times 10^{-6}$) was (6.7×10^{-5}), which was noticeably greater when compared to cashiers (1.1×10^{-5}). According to the study, exposure to benzene potentially has raised 70.67% of cancer risk. A prior research (93) used cohort data from US industry workers to quantify exposure and compute the standardized mortality ratio (SMR). The 200 ppm-year exposure group did not have a higher risk of AML, while those who had 200 ppm-year exposure or more had significantly higher SMRs (95% CI) for AML. In the groups exposed to 200–400 ppm/year and more than 400 ppm/year, the SMRs (95% CI) for AML were 27.2 (3.3–98.0) and 98.3 (20.3–287.3), respectively. It was concluded that benzene was linked to all forms of lymphohematic carcinogenesis. Additionally, the risk level for hematopoietic cancer will be determined by the cumulative exposure level to benzene, which is comparatively lower at 0.5–1 ppm-year.

2.6.4.1. Effect of Benzene on HSCs and MSCs

According to reports, benzene may have several different ways of acting on the hematopoietic stem cell (HSC) niche, a complex milieu that is home to HSCs as well as multilineage hematopoietic stem and progenitor cells (HSPCs). By inducing chromosome aberrations, oxidative stress and apoptosis, aberrant deoxyribonucleic acid (DNA) repair mechanisms and epigenetic alterations, DNA damage, and changes in gene expression regulating self-renewal and differentiation, benzene causes genotoxicity, leukemogenicity, and hematotoxicity in exposed HSPCs (94). Exposure to benzene changes HSC differentiation and causes apoptosis. Benzene metabolites produced by metabolism in the liver and bone marrow harm HSCs, A growing body of research indicates that benzene and its metabolites are toxic to HSCs, causing both immediate and long-term harm to HSPCs (progenitors) as well as alterations to the hematopoietic microenvironment in bone marrow. The BM niche, a particular milieu made up of various hematopoietic stem cells, stromal cells, extracellular matrix, and cytokines—the elements and their interactions comprise a distinct hematopoietic

microenvironment—is harmed by benzene and its metabolites (95). MSCs, or mesenchymal stem cells, are important in the BM microenvironment and have an impact on the pathophysiology of AML. MSCs offer apoptosis protection in AML, and soluble mediators and cell-cell contacts are key components of the two-way communication between leukemia cells and MSCs. AML-MSCs differ from their normal counterparts in several ways, and changes in the marrow environment may be a factor in leukemogenesis. Improved adipogenic potential and adipogenic niches are

displayed by AML-MSCs, which also stimulate tumor development by causing lipolysis and supplying leukemia blasts with fatty acids, which increases their survival. Targeting these MSC adipogenic pathways may interfere with the pro-tumoral microenvironment, offering a possible treatment approach (96) (97). Benzene causes bone marrow failure (BMF), and its hematotoxicity is linked to immunological oxidative stress responses that are triggered by the generation of reactive oxygen species (ROS). Benzene exposure has also been linked to abnormal gene alteration, which is another effect of the carcinogen. Changes in benzene-induced gene expression were noted following benzene exposure therapy. Benzene exposure's suppressive impact on hematopoietic cells was linked to aberrant gene expression profiles in signal pathways implicated in inflammation and DNA damage (98).

2.7. Current Treatment Methods & Drugs Used to Treat AML

Strong basic and translational research has been conducted on AML, and within the last (10-15) years, the knowledge of the pathobiology and genetic variety of AML has significantly increased. Between 2017 and 2019, the FDA approved eight medicines for the treatment of AML, and this work resulted in the development of several novels, promising therapeutics for the disease. Specifically, the molecular landscape of AML has been better understood because to large-scale genomic investigations. This includes the impact of many recurrent mutations and clusters of co-occurring mutations that often have prognostic and, in certain situations, therapeutic significance (99). In preclinical models, different approaches have been tried to treat different forms of cancer. For many years, the primary treatment for AML was traditional chemotherapy with cytotoxic drugs. However, the discovery of significant genetic changes by next-generation sequencing (NGS), a novel molecular technology, has opened the door for the creation of new drugs that specifically target those gene abnormalities. Treatment for AML has shifted quickly in recent years owing to the introduction of innovative medicines that target gene mutations, the identification of minimum residual disease (MRD) by flow cytometry and next-generation sequencing (NGS), and more customized cytogenetic and molecular interactions (100). Additionally, since novel medicines such as venetoclax, midostaurin, gilteritinib, quizartinib, gemtuzumab ozogamicin (GO), ivosidenib, enasidenib, and CPX351 have been introduced, traditional induction therapy like the "7+3" regimen have been improved. The current treatment paradigm uses chemotherapy that induces remission, along with cytarabine and anthracycline, either with or without a purine analogue. For example, 7 days of standard-dose cytarabine plus 3 days of anthracycline (i.e., "7 +

3"), fludarabine–Ara-C–granulocyte colony-stimulating factor–idarubicin, or similar induction, is followed by consolidation chemotherapy and/or allogeneic stem cell transplantation (SCT) for patients who have a high risk of relapse. Complete remission (CR) has been achieved in 60–80% of patients under 60 years of age using this method for the past 40 years (101) (102). Despite being successful, this method may not be well tolerated, by patients who have comorbidities, low performance status, or advanced age and are more likely to die during induction. Moreover,Conventional chemotherapy has shown inadequate response rates in high-risk genetic alterations, such TP53. For patients over 65 Treatment is done by conventional induction chemotherapy regimen, commonly known as 7+3, consists of three days of anthracycline and seven days of cytarabine. Achieving CR is the aim; it is successful in 40–60% of persons aged 60 and more, compared to 60–80% of younger adults (103). The predicted 10-year survival rate for AML treated with fludarabine, high-dose cytarabine, and gemtuzumab ozogamicin (GO) is ≥75%. Better outcomes are being obtained with regimens that include high-dose cytarabine, adenosine nucleoside analogs, and GO than with the "3+7" regimen (3 days of daunorubicin + 7 days of cytarabine), which has less favorable results in younger/fit patients (estimated 5-year survival rates of 35%; worse in real-world experience). Preliminary results from the addition of venetoclax, FLT3, and IDH inhibitors totheseregimens are favorable. The new standard of care for elderly or unfit individuals is low-intensity therapy using venetoclax and hypomethylating drugs (HMAs) (104).

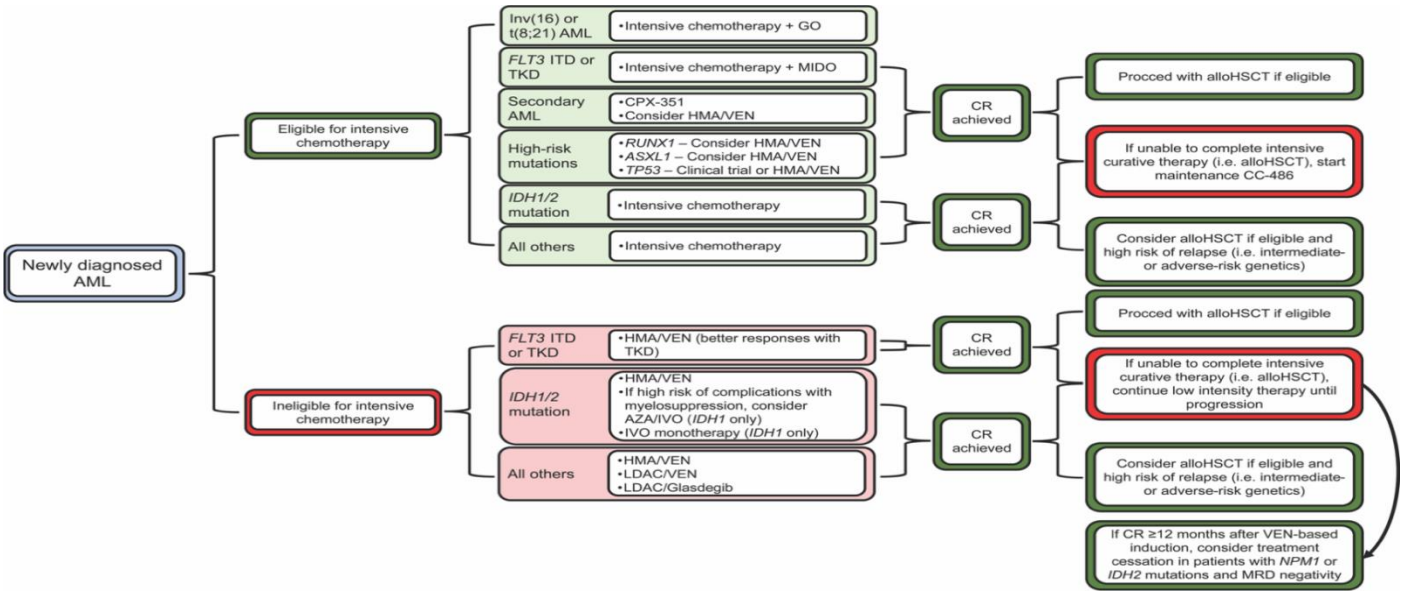

Figure2.4 Treatment of AML with FDA approved therapies (105)

2.8. Ashwagandha

Other names for Indian ginseng include Vitania sluggard (Withania somnifera), Ashwagandha, and Indian winter cherry. The term "Ashwagandha" comes from the word "ashwa," which means horse, and the root is the raw material utilized in medicine. It is said that ingesting the root gives one abilities akin to those of a horse.

The distinctive scent of the plant's new roots is referenced by the second component of the name, "gandha," which means fragrance (106). The anti-stress, anti-inflammatory, antimicrobial, anti-cancer, anti-diabetic, anti-obesity, cardio protective, and hypolipidemic qualities of ashwagandha are now established. Its qualities in the fields of neurology and psychiatry—particularly Alzheimer's disease, Parkinson's disease, multiple sclerosis, depression, bipolar disorder, insomnia, anxiety disorders, and many more—are especially intriguing. Because W. somnifera has the ability to inhibit coronavirus, its active ingredients also gained popularity during the SARS-CoV-2 pandemic. Additionally, consideration should be given to ashwagandha's impact on the hormonal system (107).

2.8.1. Phytochemicals Components

Withania somnifera has diverse phytochemical constituents, and is unique as it possesses steriodal alkaloids and lactones and flavonolides tannins and phenolic (108).Withanolides has an ergostane skeleton and polyoxygenated steroid classification, withanolides are a chemical class of naturally occurring steroidal lactones. Withanolides typically have oxygen atoms at positions C-1, C-22, and C-26, as the main chemical components of WS (109). Ashwagandha contains Alkaloids like somniferine, anaferine, and cuscohygrine contribute to the plant’s sedative and adaptogenic effects, helping in the management of stress and anxiety (110). Ashwagandha`s Flavonolides contribute to ashwagandha’s neuroprotective and anti-inflammatory effects. These compounds are being studied for their roles in managing stress, enhancing cognitive function, and offering protection against oxidative stress (111). Sterols Include β-sitosterol and ergosterol as key sterols, their antioxidant, anti-inflammatory, and immune-modulating activities, and their therapeutic potential in metabolic disorders and cardiovascular health (112)**.** Tannins are water soluble phenolic compounds with a molecular weight between 500 and 3000 Daltons and may be chemically classified into two groups: hydrolysable tannins and condensed tannins. Hydrolysable tannins are connected by ester-carboxyl linkages, which undergo hydrolysis under acidic and basic conditions (113). Phenolics in ashwagandha are molecules that can act as antioxidants to prevent heart disease, reduce inflammation, lower the incidence of cancers and diabetes, as well as reduce rates of mutagenesis in human cells (114).

2.8.2. Effect of ashwagandha on mood changes

The therapeutic effects of Ashwagandha are primarily attributed to its bioactive compounds rather than its nutritional content alone. Ashwagandha is also considered an adaptogen that helps to restore homeostasis by counteracting external stimuli as nonspecific regulators, via several mechanisms of action associated with the homeostatic preservation of the hypothalamicpituitary-adrenal (HPA) axis and the regulation of key mediators of the stress response(115). The major, pharmacologically important chemical constituents of the ashwagandha plant are the steroidal lactones and their glycosides, collectively known as withanolides .In animal stress models,

ashwagandha has been shown to possess anxiolytic, antidepressant, and neuroprotective effects. Ashwagandha root extract (ARE) was reported to reduce stress in obese adults under chronic stress and anxiety and cortisol levels in chronically stressed adults (116). Ashwagandha has the antioxidant property that can reduce free radicals induced oxidative stress. . Thus, some of the useful effects of dietary intake Ashwagandha roots on triglyceride level are attributable to the reduction of stress oxidative and lipid peroxidation. Hormones regularly occur as men age (117). Research suggests that ashwagandha may have a beneficial effect on reducing stress levels. Its adaptogenic properties may help the body better cope with stress and regulate levels of cortisol, the stress hormone. In addition, ashwagandha has shown the potential to improve mental well-being and cognitive function, which may further help reduce perceived stress (118).

2.8.3. Effect of ashwagandha on inflammation

Inflammation is a model defensive attitude to tissue harm provoked through trauma, pathogens and irritants. Rheumatoid arthritis (RA) is classified as an inflammatory disorder that creates synovial joints' inflammation. It is linked to the growth of synovial cells and the infiltration of stimulated inflammatory cells, like macrophages, plasma cells, and memory T cells, which eventually destroys the cartilage and bones (119). Evidence from research studies shows that the central nervous system (CNS) and the immune system respond to physiological and psychological stressors through multiple pathways which result in by result in accentuated expression of the inflammatory mediators, ie, the pro-inflammatory cytokines. The immune system further responds to these stressors and communicates with the CNS that results in elevated pro-inflammatory cytokine levels (120). Ashwagandha has been reported to possess an extensive spectrum of pharmacological activity, including analgesic, anti-inflammatory, sedative, hypotensive, anxiolytic, immunomodulatory, central nervous system, cardiac, anabolic, and antioxidant properties. Moreover, it increases thyroid activity and respiratory function, and relaxes smooth muscle (121). It is known that anti-inflammatory drugs have a beneficial effect on cancer treatment, but theireffect is limited by the side effects they cause. This is the reason why researchers began to look for other alternatives for treatinginflammation that causes tumorigenesis. Withania somnifera has piqued the curiosityofresearchers. It has the effect of modulating signaling pathways: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (122). Previous studies reported that ashwagandha is known to have anti-inflammatory properties by preventing the initiation of adverse processes of sciatic nerve morphology, and internal cell functions leading to improved coordination, behavioral and physiological functions in alloxaninduced diabetic rats (123).

2.8.4. Effect of ashwagandha on cancer

Cancer is the second major cause of disease related death worldwide and the global incidences are increasing at a very rapid pace. The problem in detection, development

of chemoresistance, highly aggressive nature of cancer cells, and frequent relapse of tumors result in the complex biology of the tumor and thus presents a challenge to the researcher to treat the disease. In fact cancer therapeutics have the lowest clinical trial success rate in comparison to other major diseases (124). In addition, Withania somnifera has shown antiproliferative effects, reducing oxidative stress, inhibiting cyclooxygenase-2, inducing targeted cytotoxic effects on cancer cells, and also exhibiting anti-angiogenic activity. In this paper, we will focus on the impact of Ashwagandha on cancer treatment leukemia cancer as an example, based on available medical literature and the latest scientific research (125).

2.8.5. Effect of ashwagandha on leukemia

Withania somnifera root aqueous extract (WRE) was proved to effectively modulate antioxidant activity, inflammatory cytokines, and cell death in human leukemia monocytic cell line (THP-1 cells). WRE was also found to decrease proinflammatory cytokine levels which may relieve cachexia due to cancer and excessive leukemic cell growth (126). Withanolide D, a bioactive compound in Ashwagandha, has been shown to promote apoptosis (programmed cell death) in leukemia cells. Research involving leukemic murine models found that Withanolide D decreased the viability of leukemia cells and increased pro-apoptotic activity by upregulating PUMA and downregulating BCL2, key proteins involved in apoptosis regulation (127). WS (Ashwagandha) that get high reputation cytotoxicity against leukemic cells from cell lines and patients with acute myeloid leukemia (128). Withanolide D is a steroidal lactone isolated from W. somnifera. WND has been reported to exhibit strong antileukemic effects through the induction of cell death and apoptosis in both dose-dependent and time-dependent manners in myeloid leukemia K562 cells, in the lymphoid leukemia MOLZ-4 cells, and in primary cells derived from leukemia patients. In addition, WND inhibited tumor growth in K562 xenograft nude mice, and resulted in significant reduction of both tumor size and volume. Importantly, WND did not appear to cause any adverse effects (129).

2.9. Curcumin

One of the most common traditional spices we use on a daily basis in our cuisine is turmeric. In addition to being used as a spice, it has been utilized for centuries in medicine for anti-inflammatory, antibacterial, antioxidant, and skincare applications. However, because to Curcumin (Hcur), a naturally occurring polyphenolic active component, turmeric has gained a whole new significance in medicinal chemistry and pharmacy this decade as a possible cytotoxic agent against cancer cells. According to a study, curcumin inhibits the activity of the transcription factor NF-κB, which causes tumor cells to undergo apoptosis (130).

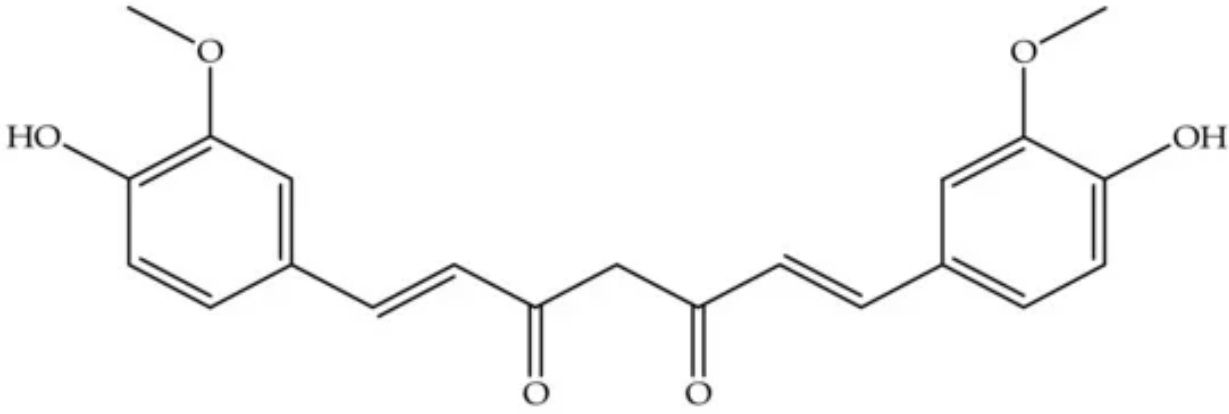

Figure 2.5 chemical structure of curcumin

2.9.1. Phytochemical Components of Curcumin

The presence of phytochemical agents such as saponins, tannins, phenolics, flavonoids, terpenoids, cardiac glycosides, and alkaloids was shown by a qualitative phytochemical study of turmeric extract (131).When polyphenolis are employed therapeutically, encapsulation can also be employed to increase solubility, minimize degradation, lower toxicity, and regulate absorption and the resulting biological response. Curcumin (CUR) (Figure 1) is one of the bioactive compounds that has received the most attention up to this point because of its alleged anti-oxidant, anti-inflammatory, and anticancer properties. However, because of its low water solubility and poor stability in GIT fluids—more especially, in alkaline pH conditions—CUR is poorly absorbed from the gastrointestinal tract (GIT) after oral administration (132). Numerous saponins such as the ones existing in curcumin have been identified, refined, and are becoming more popular in cancer treatment. The considerable structural diversity of saponins is associated with their anticancer properties (133). Tannins are found in curcumin which are phenolic compounds; they are abundant and nearly universal throughout the vegetative kingdom. They have been used for generations to treat a wide range of illnesses and ailments, which has compounded their historic role in leather in popular medical and pharmaceutical legend (134). flavonoid are broad family of polyphenols known as flavonoids Anti-inflammatory, antioxidant, antiviral, antibacterial, anticancer, cardioprotective, and neuroprotective actions are only a few of their many biological qualities (135). Terpenoids are the most varied are terpenoids, which have important characteristics when considering chemical ecology (136). Bioactive substances called terpenoids have a range of pharmacological properties, including anticancer properties (137). Cardiac Glycosides are natural steroid substances called cardiac glycosides (CGs) are found in both plants and animals. They have long been recognized as cardiotonic drugs that are frequently used to treat a variety of cardiac conditions because they decrease the action of the Na+/K+-ATPase (NKA) pump and alter the contractility of the heart muscle (138). Alkaloids are distinctive, specialized metabolites with a wide range of biological functions (139). Because alkaloids are a potentially novel class of natural antibiotic with a broad antibacterial range, infrequent side effects, and a low propensity to develop drug resistance, considerable research efforts are concentrated on them. Inhibition of bacterial cell wall formation, alteration of cell membrane permeability,

inhibition of bacterial metabolism, and inhibition of nucleic acid and protein synthesis are their primary antibacterial mechanisms (140).

2.9.2. Anti-Inflammatory Effect of Curcumin

Numerous preclinical and clinical research in a range of inflammatory illnesses have confirmed curcumin's anti-inflammatory qualities.
Curcumin is regarded as a promising medication candidate for the treatment of inflammatory illnesses because of its anti-inflammatory qualities. The body's reaction to specific stimuli, like bacterial or viral infections, mechanical harm, or an overreaction by the immune system, is inflammation. Excessive inflammatory reactions can result in tissue damage, organ failure, and potentially fatal diseases, yet the inflammatory response aims to eliminate stimulating substances and speed tissue repair (141).By controlling a variety of transcription factors and cytokines associated with inflammation, curcumin has a well-established anti-inflammatory effect. Since inflammation is a condition that underlies cardiovascular illnesses, curcumin may be used as a treatment likewise (142).

2.9.3. Anti-Inflammatory Mechanism of Curcumin

Inductors, sensors, mediators, and effectors are the four components that make up the inflammatory pathway. distinct inflammatory stimuli cause distinct and as-yet-undefined physiological and pathological pathways of inflammation. Reversing the medium's effect on the target tissue, producing anti-inflammatory mediators, controlling the target tissues' reaction to inflammatory mediators, and acting on receptors and signaling pathways are the main ways that medications generally have anti-inflammatory effects (143).

2.9.4. Antioxidant

Because CU's molecule contains phenolic groups, it has an antioxidant nature and is electroactive (144). Curcuminoids (curcumin I, II, and III) and non-curcuminoid chemicals make up the majority of turmeric's bioactive components. Strong antioxidant properties of curcumin have been demonstrated to help prevent OS and a number of chronic illnesses. Free radicals (FR) are unstable chemicals that harm cells and play a role in the development of chronic diseases like diabetes, cancer, and heart disease. Curcumin is a potent scavenger of FR. Significant biological activity is also exhibited by non-curcuminoid molecules, which have been linked to anti-inflammatory, antioxidant, and anticancer qualities (145). Curcumin's antioxidant, chelating, and hypertension-inhibiting properties can help prevent diabetes, heavy metal absorption, and hypertension.6,57 Additionally, curcumin and many of its complex forms activate glutathione S-transferase and inhibit the production of free radicals, such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS), which scavenge free radicals and release antioxidants to stop lipid peroxidation (146).Several studies have also documented the antioxidant properties of C. longa and CUR. CUR and plant extracts raised thiol and superoxide dismutase levels while lowering malondialdehyde and nitric oxide levels (147).

2.9.5. Anticarcinogenic Effects of Curcumin

Curcumin, a natural component, has been shown to have anti-cancer activities in both preclinical and clinical studies. Preventing tumor growth, angio genesis, and carcinogenesis are some of curcumin's anti-cancer qualities (148). By triggering apoptosis and preventing T47D cells from progressing through the cell cycle, the turmeric ethanol extract demonstrated a possible anti-cancer activity (149). Curcumin may reduce proliferation by slowing down the cell cycle by blocking the Wnt/β-catenin pathway, raising p53, p21, and p27 levels, and subsequently lowering CDK4 and Cyclin D1 levels. By reducing the TGF-β/Smad2/3 pathway, curcumin may increase the levels of E-cadherin and reduce those of N-cadherin, vimentin, fibronectin, slug, and snail, thereby preventing migration and invasion. By triggering the p38 MAPK, JNK, and ERK pathways, curcumin may increase the generation of ROS (150). Pure curcumin may be useful in leukemia treatment since it exhibits promise in modifying the expression of the WT1 gene (151).

2.9.6. Anti- Leukemic Effects of Curcumin

Curcumin stops multidrug resistance (MDR) and causes malignant cells to undergo apoptosis. A pharmacological effect on MM was brought about by mounting evidence about curcumin's therapeutic qualities. Curcumin has been shown to disrupt oncogenes, cell cycle checkpoints, and a number of signaling pathways. We outlined curcumin's anti-MM properties in this research (152). Curcumin increased the expression levels of the ISG3 transcription factor complex, which activated caspase 1, enhanced cleavage of GSDMD, and caused pyroptosis. This in turn caused the activation of AIM2, IFI16, and NLRC4 inflammasomes in leukemia cells U937 (153). Curcumin's promise as a therapeutic agent is highlighted by its ability to induce apoptosis, inhibit cell proliferation, and prevent the spread of AML cells (154). By upregulating DR4 and DR5 expression and suppressing cFLIP and anti-apoptotic proteins Mcl-1, Bcl-xl, and XIAP, curcumin enhances TRAIL-apoptotic signaling in leukemic cells (155). Curcumin inhibits the spread of cancer via lowering matrix metalloproteinase levels. Curcumin inhibits the growth of hematological malignancies by decreasing several downstream targets, such as VEGF, Akt, and STAT3. Curcumin decreases cancer cells' resistance to radiation and promotes DNA damage (156). A research employing cell lines from acute promyelocytic leukemia (HL-60) and chronic myeloid leukemia (K562) demonstrated that curcumin treatment stops the cell cycle in HL-60 cells at G1 and in K562 cells at G2/M. Curcumin's effects on the control of cell death in cell lines originating from acute and chronic myeloid leukemia were also shown to have different biological pathways. Curcumin-induced cell death in HL-60 cells was dependent on caspase, but cell death in K562 cells was caspase-independent. In summary, curcumin acts on myeloid leukemia cells by distinct cellular pathways in both acute and chronic forms, and its effective antitumoral impact was stronger in K562 cells than in HL-60 cells (157).

2.10. Green Tea

Originating in East Asia, tea is now the most popular beverage drunk globally, second only to water. The Camellia sinensis plant yields green, black, and oolong teas, although each has distinct qualities. In Asian nations, such as China, Japan, and

Korea, green tea is the most popular beverage and makes up 20% of all tea drank globally. The daily consumption of green tea ranges from three cups on average to up to ten cups. A human adverse event report states that the reported safe amount of green tea is 704 mg of epigallocatechin-3-gallate (ECGC)/day, or roughly 880 mL of brewed green tea per day (158). Green tea (Camellia sinensis) is the most consumed tea globally, with epigallocatechin gallate (EGCG) as its primary active component. EGCG exhibits chemo preventive properties against various cancers, including breast, colon, and prostate cancer. Its complex mechanism allows it to act as both an antioxidant and prooxidant, influencing pathways related to apoptosis, lipid peroxidation, and free radical scavenging. This paper reviews EGCG's chemical and biological characteristics and its potential therapeutic effects on benign reproductive diseases in women (159). Green tea might be useful in preventing leukemia. It is well recognized that several carcinogens can be detoxified by glutathione S-transferases (GSTs). We looked into the effects of green tea consumption and GSTM1, GSTT1, and GSTP1 polymorphisms on adult leukemia risk, as well as if these relationships differed amongst GST genotypes (160). Numerous studies have been conducted to evaluate the antibacterial potential of green tea catechins. A wide variety of aerobic and anaerobic bacteria, viruses, fungi, and at least one parasite are among the organisms that green tea affects . Green tea is thought to have antimicrobial properties through the following mechanisms: bacterial cell membrane damage, bacterial fatty acid synthesis inhibition, inhibition of other enzymes (such as protein tyrosine kinase, cysteine proteinases, DNA gyrase, and ATP synthase), and inhibition of efflux pump activity (161).

2.10.1. Chemical Composition of Green Tea

Green tea leaves contain biomolecules, such as catechins and flavonoids that reduce Ag ions to Ag and stabilize silver nanoparticles (AgNPs). These compounds act as electron donors, preventing antioxidants from becoming free radicals, which facilitates the formation of AgNPs. Additionally, green tea extract serves as a stabilizer during AgNP synthesis. Previous studies have demonstrated that AgNPs can be produced by simply heating green tea extract at 50°C (162). Catechins are members of the flavan-3-ols family and comprise 60–80% of tea polyphenols. They have a C3–C6–C3 flavonoid structure. They are (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechingallate (ECG), and (−)-epigallocatechingallate (EGCG). Of these, EGCG is the most prevalent, accounting for as much as 50% of the flavanols. Quercetin, kaempferol, and myricitin are examples of flavonols that are usually glycosylated with rhamnose and glucose. After fermentation, as flavan-3-ols oxidize or break down, these chemicals become more important. The most prevalent flavonol in tea is quercetin-3-rutinoside (163). About 15–25% of green tea is protein, which includes amino acids including tyrosine, tryptophan, and L-theanine. There are two types of its protein: complete and incomplete. Green tea also contains trace amounts of iron, calcium, and magnesium, as well as carbs like sucrose and glucose. Sterols, lipids (linoleic and linolenic acids), and vitamins A, B, C, and E are also abundant in it. Sencha tea (4 mg) and Gyokuro

tea (around 10 mg) have the highest nutritional contents (164). The primary bioactive components that give green tea its distinct health advantages are its polyphenols, also referred to as catechins. There are both simple and complex polyphenols in green tea. Catechins and flavonols are the flavonoid monomers that make up the majority of the polyphenols in green tea. Flavonoids can help tea lessen the harmful effects of reactive oxygen species (ROS) and oxidative stress, and they are important in the prevention and treatment of human diseases (165). It has bioactive substances, particularly polyphenols that improve health. Green tea polyphenols possess antibacterial, anti-inflammatory, and antioxidant properties that may improve oral health and help manage rheumatoid arthritis (RA) symptoms. Regular oral care is recommended for RA patients. This study explores green tea oral care solutions to enhance hygiene and potentially slow RA progression also they can inhibit the growth of various bacteria (166).

2.10.2. Antioxidant Properties of Green Tea

Antioxidants like polyphenols, which contain a wide range of chemicals like flavonols, flavandiols, and phenolic acids and can make up as much as 30% of dry mass, are responsible for the demonstrated health benefits of green tea. Green tea consumption is linked to a lower risk of circulatory system diseases and cancers by delaying the occurrence of factors associated with the progression of those illnesses. This is because of its antioxidant, antiviral, and anti-inflammatory properties, which stimulate immunological and detoxification processes. The kind, quantity, temperature, and brewing time of tea all affect how many healthful components are present (167). Green tea lowers the risk of cancer , boosts fat burning, enhances physical performance, and may preserve the brain as we age, reducing the incidence of Parkinson's and Alzheimer's disorders . It can reduce the risk of infection, eliminate bacteria, and enhance oral health. It may also reduce the chance of developing diabetes and heart disease. Weight loss may benefit from it. It exhibits properties including anti-cancer, antihypertensive, anti-diabetic, and antioxidant (168). Green tea is a 'non-fermented' tea and contains more catechins than black tea or oolong tea. Catechins are in-vitro and in-vivo strong antioxidants.In addition, its content of certain minerals and Vitamins increases the antioxidant potential of this type of tea (169).

2.10.3. Effects of Green Tea on inflammation

Polyphenols, often known as catechins, are the most potent ingredients in green tea . Numerous polyphenolic components, which have antimutagenic,antioxidant and anti-inflammatory properties, are abundant in green tea . The main polyphenol in catechin green tea extract (GTE), epigallocatechin-3-gallate (EGCG), is essential to the anticancer properties of green tea polyphenols. According to recent research, EGCG exhibits anticancer properties in haematopoietic malignancy. The study found significant increases in WBC counts (leukocytosis) and decreases in RBC counts, hemoglobin, and platelet counts in benzene-treated albino rats, indicating successful leukemia induction via benzene Chromasolve injections. Treatment with Moringa

oleifera, curcumin, green tea extract (GTE), and cyclophosphamide resulted in decreased WBC counts and increased RBC counts, hemoglobin, and platelet counts across all treatment groups. This suggests potential anti-leukemic properties of these natural products comparable to conventional drugs like cyclophosphamide (170). There are several theories as to how green tea contributes to weight loss. Reduced food intake, disruption of lipid emulsification and absorption, inhibition of adipogenesis and lipid synthesis, and an increase in energy expenditure through thermogenesis, fat oxidation, and faecal lipid excretion are some of these mechanisms.8. Furthermore, prior laboratory and clinical research indicates that dietary polyphenols have anti-inflammatory properties. By lowering nuclear factor-κB expression and proinflammatory cytokine production, green tea extract (GTE) has anti-inflammatory properties. It has recently been suggested that polyphenol chemicals like catechins are primarily responsible for the beneficial properties of green tea (171). Since most studies have concentrated on the effects of green tea EGCG on hard tissue degradation, it is still unknown exactly how it mediates inflammation in oral tissues. It is crucial to investigate green tea polyphenols' potential to prevent cytokine-driven inflammation in oral cells, as they have been investigated for their anti-inflammatory properties in other cell types and animal models.For 24 hours, cells were pretreated with different doses of GTE (1, 2.5, 5, and 10 mg/ml) and LPS (1 μg/ml) to see if GTE suppresses the expression of inflammatory genes produced by LPS. Compared to cells that were not treated, LPS administration dramatically boosted the production of IL-31, IL-6, and TNF-α by about ten times. These cytokines were decreased by approximately 8 times at GTE doses of 2.5, 5, and 10 mg/ml in comparison to the LPS-only control. Additionally, ELISA analysis confirmed the RT-PCR results by demonstrating significant decreases in IL-1β, IL-6, and TNF-α protein levels in GTE-treated groups (172).

2.10.4. Effect of Green Tea on Cardiovascular health

Green Tea may aid in cancer, metabolic disorders, neurological diseases, and cardiovascular diseases (CVD). Regular consumption is associated with lower blood pressure and better endothelial function, potentially reducing cardiovascular events. However, recent studies find no causal link between green tea drinking and CVD outcomes. Nonetheless, habitual tea drinkers generally have a lower risk of heart disease and longer life expectancy (173). According to observational research, green tea may be the main preventive measure against cardiovascular illnesses (CVD), such as atherosclerosis, coronary heart disease, and stroke. Inflammation, oxidative stress, diabetes, lipid disorders, hypertension, endothelial dysfunction, and other conventional and emerging cardiovascular risk factors have all been shown to be positively impacted by green tea products (174). Consuming green tea improves a number of health outcomes, including cardiovascular diseases (CVD) like stroke and coronary heart disease (CHD), according to population-based research conducted in the last ten years (175). The study included 24 healthy male Wistar albino rats (200–250 g) from Saki Yenilli Experimental Animals Inc. and was approved by the Giresun University Animal Research Ethics Committee. After a week of acclimatisation, the

rats were kept in a controlled setting with a 12-hour light/dark cycle. Three groups were formed out of them:For three weeks, the control group (n=8) was given regular saline.2. REM sleep deprivation for six hours was administered for 21 days to the Chronic-REM Sleep Deprivation (CRSD) Group (n=8).The CRSD + Green Tea 200 Group (n=8) was given 200 mg/kg of green tea extract every day for 21 days, but otherwise received the same treatment as CRSD and they find out how the green tea made a great effect (176).

2.10.5. Effect of Green Tea on Cancers

One condition known as cancer occurs when some body cells proliferate out of control and spread to other body regions (177). Green tea's anti-carcinogenic qualities include regulating tumor cell death, proliferation, and vascular angiogenesis in solid tumours. According to recent research, green teas naturally contain catechins, which have an inhibitory effect on NF-κB. The four main essential catechins in GT are 1) EC, (-)-epicatechin 2) (-)-epigallocatechin, EGC this study shows that the EGCG, (-)-epigallocatechin-3-gallate, and ECG, (-)-epicatechin-3-gallate, also exist. The most abundant of these catechins in green tea is EGCG (178). A number of epidemiological studies have demonstrated that drinking tea has anti-cancer effects, lowering the relative risks (RR) of numerous site-specific malignancies. Cohort studies on malignancies such as esophageal, prostate, and urinary tract tumors have revealed elevated RRs, however the results are not entirely consistent. Green tea has shown promise in treating several types of cancer, according to a comprehensive analysis of 144 randomized controlled trials and case-control studies. Green tea consumers had mixed results for different forms of cancer, for example, with an RR of 0.50 (CI = 0.18-1.36) for prostate cancer and 1.50 (CI = 0.41-5.48) for gynaecological cancer (179). EGG has been demonstrated to prevent DNA methylation and reverse epigenetic modifications in other malignancies, but its function in the treatment of HNSCC is yet unknown. With the use of in vitro and in vivo models, we examined whether EGG would reactivate repressed tumor suppressor genes and identified the molecular mechanism behind these effects using two HNSCC cell lines obtained from several sub-sites, including the oral cavity and pharynx (180).

2.10.6. Effect of Green Tea on Leukemia

Vascular endothelial growth factor (VEGF) signaling is inhibited by green tea catechins, especially epigallocatechin-3-gallate (EGCG), which has strong anti-cancer effects. Because EGCG inhibits tyrosine kinase, it lowers VEGF receptor phosphorylation and, in turn, p-STAT3, which causes B cells with chronic lymphocytic leukemia (CLL) to undergo apoptosis. EGCG therapy promoted processes like apoptosis and cell cycle arrest in xenograft models, reducing tumor weight and development without causing adverse effects. Competition with haematopoietic growth factor receptors is another aspect of this "EGCG sealing effect." Green tea extract's ability to induce apoptosis may also be linked to its suppression of proteasomal function, which raises ubiquitinated protein levels. Protease-like activity of proteasomes is strongly and selectively inhibited by EGG (181). The most common malignancy is acute lymphoblastic leukemia, which has a

high cure rate of over 90% for B-cell ALL and over 80% for T-cell ALL. Despite this, B-ALL exhibits substantial genetic variation, with more than 20 different subtypes found. Though its benefits on pediatric B-cell ALL have not yet been documented, the green tea ingredient epigallocatechin gallate (EGCG) has demonstrated promise in preventing the proliferation of cancer cells, notably in myeloid leukemia. Because of its ability to trigger apoptosis and stop the advancement of the cell cycle, EGCG has the potential to be a therapeutic agent (182). Other polyphenols have also been shown to have anti-leukemic actions against AML cells, such as resveratrol from wine, epigallocatechin-3-gallate from green tea, genistein from soybeans, lycopene, and quercetin (183). With a poor prognosis, frequent recurrences, high mortality, and minimal treatment efficiency, leukemia accounts for 8% of all cancers. Resveratrol (RES), curcumin (CUR), and EGCG are examples of polyphenols that have been examined for their anti-leukemic actions in vitro, although there is little study on their effects in vivo. Because of its anti-inflammatory and antioxidant qualities, RES has promise as an adjuvant treatment. Inducing apoptosis and modifying autophagy in leukemia cells, it lessens the adverse effects of medications such as barasertib and everolimus. RES also mitigates drug resistance via controlling MRP1 expression and the PI3K/Akt/Nrf2 pathway, as well as by reducing MDR1 protein with prednisolone.By triggering apoptosis and preventing invasion in SHI-1 cells through JNK/p38 activation and ERK/NF-κB inhibition, CUR has demonstrated promise for treating acute myeloid leukemia. Additionally, it suppresses vimentin, MMP2, and MMP9 expression. EGCG demonstrates antitumor activity in leukemia, inducing apoptosis in chronic myeloid leukemia cells by regulating key signaling pathways like p38-MAPK/JNK and JAK2/STAT3/AKT (184).

CHAPTER THREE

3.0 Materials and Methods

3.1 Materials

Benzene (purity 99.9%) (Scharlau, Spain), Isopropanlol (chem lab, USA), ashwagandha and green tea extracts (Now foods, USA), curcumin extract (21 century healthcare.INC, USA), Methanol (Chem Lab, Belgium), May granwald stain (Chem Lab, Belgium), MGG (May-Grünwald Giemsa stain) (Atom Scientific, UK), Blood analyzer (Medonic M51, Sweden).

3.2 Methods

3.2.1 Experimental Design

3.2.1.1 Animal Handling

Albino healthy adult male rats aged (8-10) weeks were obtained from the Experimental Animal House, College of Science, Cihan University- Erbil. The study was approved by the Ethics Committee for Animal Experimentation, College of science, Cihan University- Erbil, Iraq. The animals were kept on a conventional pellet diet and provided with tap water. Throughout the experiments, it was ensured that all animals received appropriate care in accordance with the guidelines specified in the "Guide for the Care and Use of Laboratory Animals" issued by the National Academy of Sciences and published by the National Institute of Health.

3.2.1.2 Groupings

Thirty two male Albino rats weighing 200±20 grams were divided into four groups of six rats each, out of the thirty two rats, twenty four rats received (IV) injections of chromasolve (0.2 ml of benzene solution) every 2 alternating days for 3 weeks (185) which resulted in the death of eight rats, leaving eighteen leukemic induced rats which were divided randomly as following (G1, G2, G3, G4): (G1) was control positive group which received (IV) injections of benzene every 2 days for 3 weeks without administrating plant extracts. (G2) served as control negative group, which received normal diet. (G3) group received Benzene IV injections for 3 weeks every 2 days, following that, daily oral treatment with extract combination of (Curcumin, Green Tea, Ashwaganda) of the following doses (200mg/kg, 250mg/kg, 200mg/kg) (186,187,188) respectively for 1 month was done. (G4) rats were administrated Ashwagandha extract (300mg/kg) (189) for 1 month, following leukemia induction.

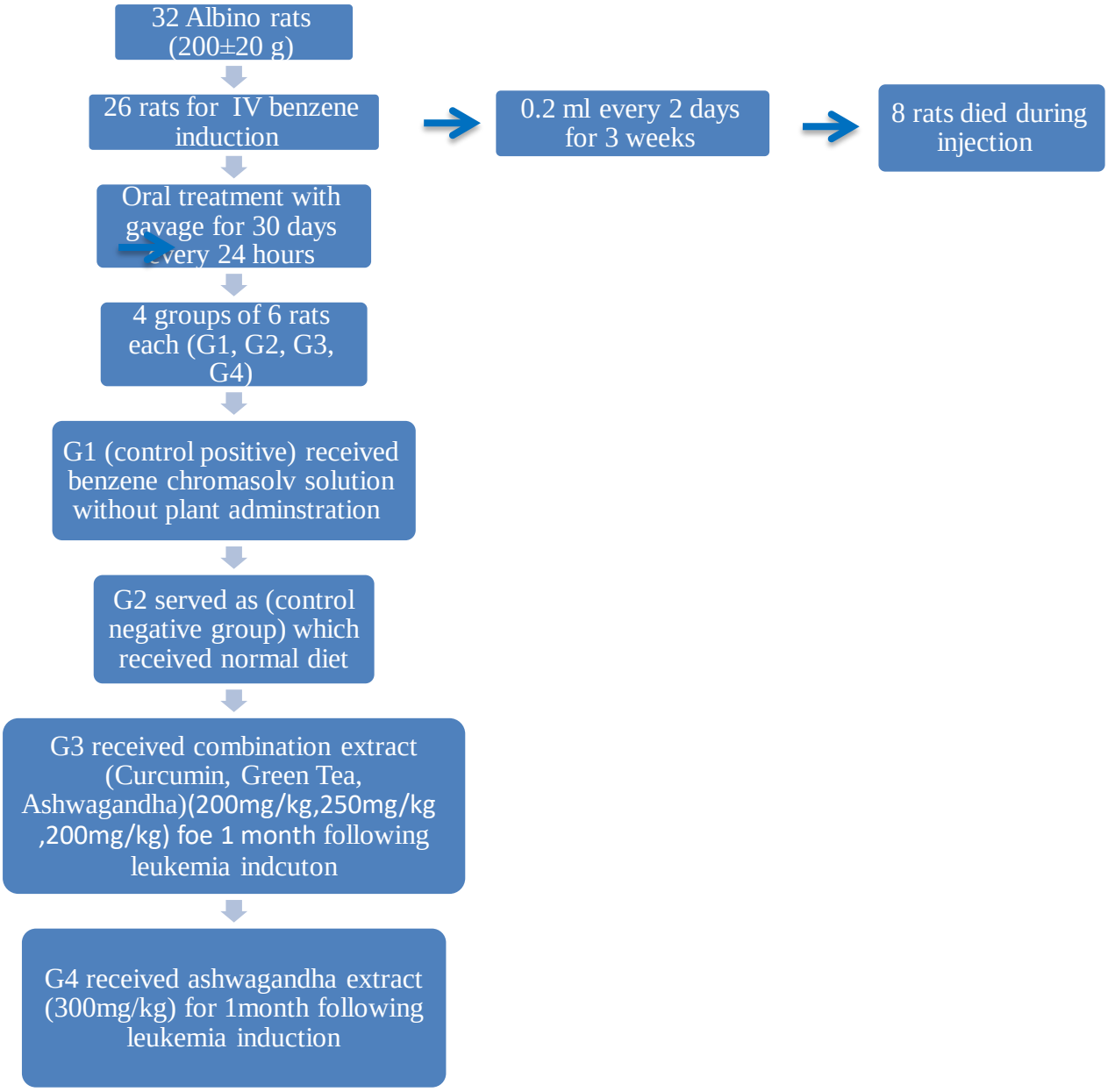

Table 3.1 Experimental design of the current study

3.2.2 Supplement Extract

Plant supplements were acquired from (Amazon.com, USA) from different manufactures, ashwagandha and green tea supplement were purchased from (Now foods, USA) with curcumin extract from (21 century healthcare.INC, USA). Ashwagandha (Withania Somnifera) extract was standardized to contain minimum (2.5% of total withanolides), while green tea extract had a standardized extract of (minimum 80% total Catechins and 50% EGCg) with up to (1%) of naturally occurring caffeine. Additionally, the used curcumin extract had a standardized extract to contain (95% of curcuminoids).

3.2.2.1 Supplement Preparation

Powder was suspended with distill water (30 ml of distilled water) on 1800 mg of ashwagandha for G3 group extract, while distill water (30 ml) was added to (1200mg, 1500mg, 1200 mg) of ashwagandha, green tea and curcumin extracts respectively for G4 group. Following the suspension of the powder, mixing with vortex at maximum speed (3000 RPM) for 10 minutes was done, prepared extract was kept in a room temperature with dry conditions during administration period. Extract preparation was carried every 72 hours to ensure stability and optimal efficacy of the extracts.

3.2.3 Administration of benzene chromasolve

Benzene was used in order to induce leukemia in the rats, with propanol as a mitigating solution; both solutions were purchased from erbil city/Iraq. Albino rats were divided into four groups, each consisting of six rats. Rats were administrated 0.2 ml solution containing benzene, distilled water, and propranolol in a ratio of (1:5:5) respectively every two alternating days for three consecutive weeks in order to induce leukemia in the rats, following induction leukemic rats were randomly assigned to three groups containing benzene treated rats.

3.2.4 Supplement Administration

The Supplement used in this research was prepared using Ashwagandha, green tea, and curcumin. Two doses were administered: the first dose consisted of Ashwagandha at 300 mg/kg, and the second dose was a combination of Ashwagandha (200 mg/kg), green tea (250 mg/kg), and curcumin (200 mg/kg) dissolved in 30 ml of distilled water for oral administration. Male albino rats weighing between 200-250 g were divided into four groups (n=6). Group 3 (G3) received oral treatment with the Ashwagandha extract for 1 month, while Group 4 (G4) was administered the combination extract of Ashwagandha, green tea, and curcumin for 1 month. Each rat in both groups received 1 ml of the respective extract orally via gavage once daily.

3.2.5 Sample Collection

Rats were used to get blood in order to investigate benzene-induced leukemia. Rats were given intramuscular injections 50 mg/kg of ketamine and xylazine for anesthesia. Ten minutes later Following that, a 5 ml syringe was used to draw blood from the heart and stored in EDTA tubes for peripheral blood smear and hematological parameters then, cervical dislocation was done to euthanize the rats and collect further samples. Following the blood collection liver, bone marrow and spleen, were collected, using a scalpel and tweezers the liver and spleen were removed for architecture study purposes. Both leg`s femoral heads were cut to harvest bone marrow, which was then cleaned from the muscles and tissues using a scalpel. For

histological investigations, all organs and samples (liver, spleen, and bone marrow) were fixed in 10% formalin until further studies were held.

3.2.6 Hematological Parameters

Following collection, blood samples were carefully stored in Ethylene diaminetetraacetic acid (EDTA) tubes to prevent coagulation and preserve cellular integrity. To minimize pre-analytical variability and ensure the accuracy of downstream analyses, samples were processed within a strict timeframe of 3 hours post-collection. An automated five-part differential blood analyzer was employed to facilitate comprehensive blood testing and complete blood counts. Studied parameters included red blood cell (RBC) and hemoglobin (HGB) counts with (HCT), as well as total white blood cell (WBC) counts and their respective differentials. All parameters were processed using open tube method.

3.2.6.1 Peripheral Blood Smear

Peripheral blood smear was used for blast cells counting. Peripheral blood was smeared on a labeled histology slide and left to be dried, following that methanol was added to the slide for 10 minutes. Following adding the slides in the methanol and left to be air dried then May Grunwald was used to stain the slides for 20 minutes, once 20 minutes has passed the slides were washed with distilled water and left to be air dried. And last stain was used to aid in staining for 20 minutes. Following that, the slides were washed with distilled water thoroughly. Once dried the slides were observed using light microscope at (100x) using immersion oil.

3.2.7 Histological Studies

A paraffin tissue processing machine was utilized to prepare the organs for architecture examination of (liver, spleen, bone marrow) tissues from each rat, which had been previously stored in 10% buffered formalin. The histopathologist examined 5-oz slices of the organs that were stained with Hematoxylin and Eosin stain

3.3 Statistical Analysis

All data were given in (mean± standard error) and analyzed by ordinary one- way (ANOVA) test using Graph Pad Prism Software (10.4.1). Data was set as significant at 95 % (<0.05) confidence level.

3.4 Ethical Approval

Ethical approval for the current study was acquired from (Cihan University- Erbil**)** for the study titled (The Combined Supplementary Impact of Ashwagandha, Curcumin, and Green Tea on Hematological Alterations in Benzene-Induced Leukemia in Albino Rats). All rats were treated humanely with minimum suffering and were provided adequate diet and water access.

CHAPTER FOUR
4.0 Results

Based on the study findings, both treatment groups Ashwagandha alone (G4) and the combination of (Ashwagandha, Curcumin, and Green Tea) (G3) demonstrated anti-leukemic effects. However, the combination treatment exhibited a slightly better overall prognosis in terms of lymphocyte and monocyte levels. The combination group (G3) had higher lymphocyte levels compared to the Ashwagandha-alone group, suggesting a stronger immune response. The monocyte count was slightly lower in the combination group (G3), which may indicate better immunological response . Blast cell counts, which indicate leukemia severity, were slightly lower in the Ashwagandha-treated group compared to the combination group though both showed significant reductions compared to the control group. exhibited better basophil regulation and a more balanced immune response .Histological studies showed better protection for bone marrow, liver, and spleen tissues, showing reduced inflammation and improved cellularity. While both treatments were effective, the combinator immune regulatory effects, making it a more promising approach overall.

4.1 Hematological Parameters

4.1.1 Total WBC

Both G3 and G4 increased total WBC counts compared to the control group, indicating strong immunostimulatory effects. While G3 showed a slightly higher WBC count, the difference between the two treatments was minimal, suggesting that Ashwagandha alone is as effective as the combination in enhancing immune response

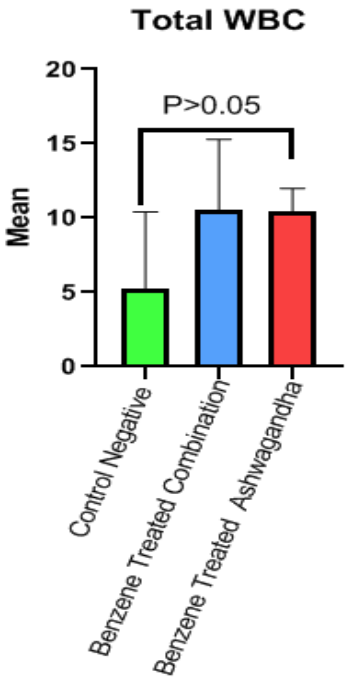

Figure 4.1 Presents total WBC means and statistical analysis

Total WBCs (4400-14800/mm^3)		
Group	**Mean**	**P value**
Control Positive(G1)	9.833±1.896	>0.05
Control Negative(G2)	5.235±2.110	
Benzene Treated Combination(G3)	10.57±1.902	
Benzene Treated Ashwagandha(G4)	10.47±0.6215	

Table 4.1 Shown total WBCs count in different groups.

4.1.2 Neutrophil

Neutrophil levels were significantly higher in treatment groups (G3 & G4) compared to the negative control (G2), suggesting an immune-boosting effect from the herbal supplements (ashwagandha, curcumin, and green tea). The low neutrophil count in G2 was increased in G3 and G4, indicating these supplements may enhance immune response and counteract leukemia-induced effects.

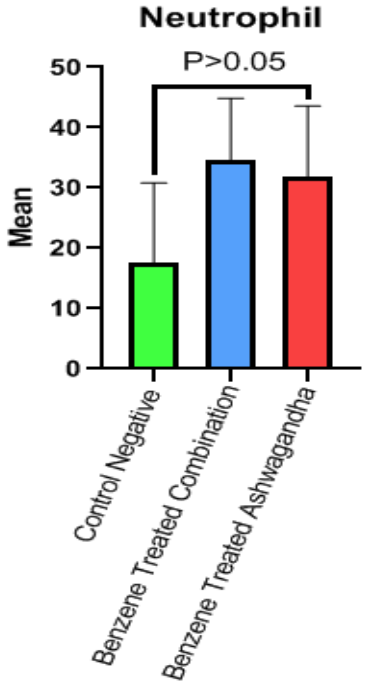

Figure 4.2 Shows statistical analysis of neutrophils

Neutrophil (13-36%)		
Group	**Mean**	**P value**
Control Positive	25.93±4.032	>0.05
Control Negative	17.58±5.406	
Benzene Treated Combination	34.70±4.137	
Benzene Treated Ashwagandha	31.87±4.779	

Table 4.2 Shows neutrophil counts in different groups.

4.1.3 Lymphocytes

Lymphocyte levels were lower in the treatment groups than in the negative control, suggesting an enhanced immune response against leukemia. Both the combination (G3) and ashwagandha-only (G4) treatments reduced lymphocyte counts, indicating immune regulation. The decline was more pronounced in the ashwagandha-only (G4) group, showing a significant difference from the negative control.

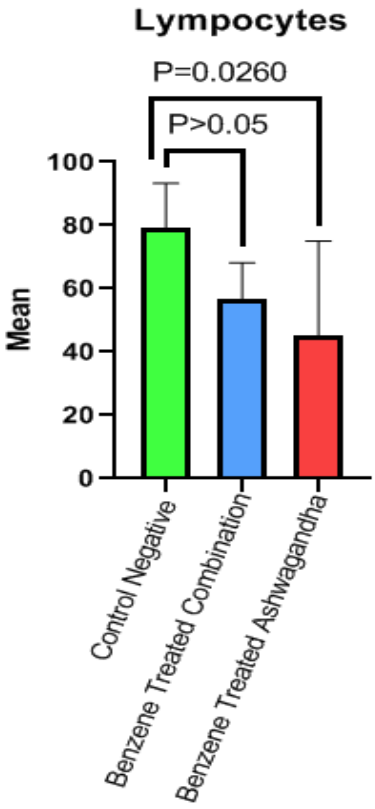

Figure 4.3 Shown lymphocytes statistical analysis

Lymphocytes (61-86%)		
Group	**Mean**	**P value**
Control Positive	65.53±1.570	*0.0219
Control Negative	79.38±5.689	
Benzene Treated Combination	56.75±4.683	
Benzene Treated Ashwagandha	45.32±12.14	

Table 4.3 Presents lymphocytes results in different groups

4.1.4 Eosinphil

Both G3 (combination treatment) and G4 (Ashwagandha alone) reduced eosinophil levels compared to the control, with G3 showing a more significant decrease. This suggests the combination treatment has a stronger regulatory effect on eosinophils, potentially improving immune modulation and reducing inflammation more effectively than Ashwagandha alone.

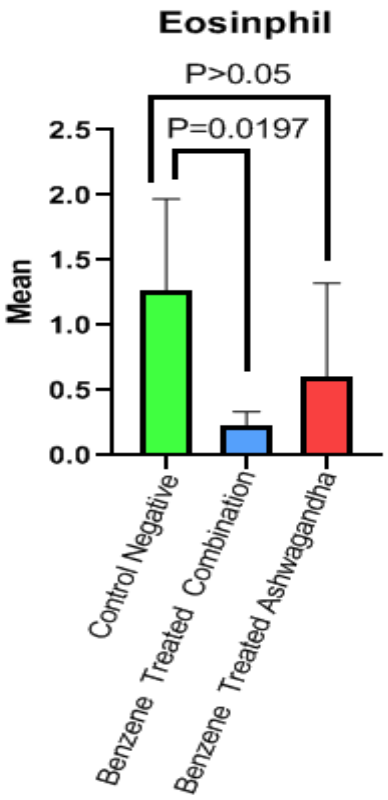

Figure 4.4 Eosinphil means and statistical analysis

Eosinophil (0-6%)		
Group	**Mean**	**P value**
Control Positive	1.200±0.2145	*0.0136
Control Negative	1.270±0.2856	
Benzene Treated Combination	0.2333±0.04216	
Benzene Treated Ashwagandha	0.6000±0.2944	

Table 4.4 Exhibited eosinophil counts in different study groups

4.1.5 Monocytes

Both G3 (combination treatment) and G4 (Ashwagandha alone) increased monocyte levels compared to the control, with G4 showing a significantly higher count. This suggests that Ashwagandha alone may more strongly stimulate monocyte production, indicating a robust immune response, while the combination treatment also contributes to immune modulation, albeit to a lesser extent.

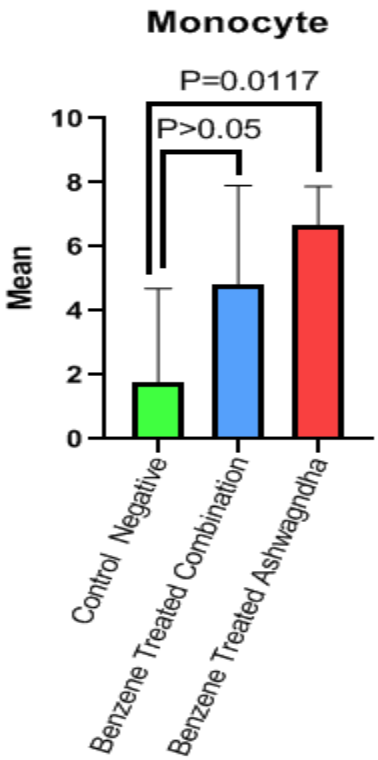

Figure 4.5 Found monocytes statistical analysis

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Monocytes (0-1%)		
Group	**Mean**	**P value**
Control Positive	8.233±2.635	>0.05
Control Negative	1.750±1.204	
Benzene Treated Combination	4.817±1.260	
Benzene Treated Ashwagandha	6.683±0.4868	

Table 4.5 Presents monocytes count in all study groups

4.1.6 Basophil

The combination treatment (G3) significantly increased basophil levels compared to Ashwagandha alone (G4) and the control group, suggesting a stronger immune-modulating effect. Ashwagandha alone (G4) had a milder impact on basophils. This indicates that the combination treatment may be more effective in regulating immune responses involving basophil activity.

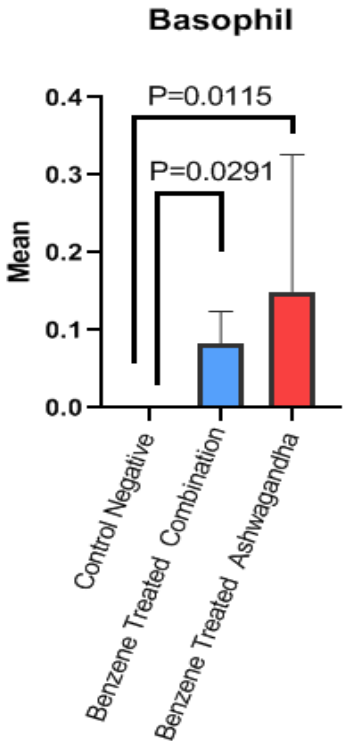


Figure 4.6 shown basophil means and statistical analysis

Basophils (0.0-1%)		
Group	**Mean**	**P value**
Control Positive	0.1000±0.04472	*0.0181
Control Negative	0.000±0.00	
Benzene Treated Combination	0.8333±0.1500	
Benzene Treated Ashwagandha	0.1500±0.07188	

Table 4.6 Shown basophil means of current study groups

4.1.7 Blast Cells

Both G3 (combination treatment) and G4 (Ashwagandha alone) significantly reduced blast cell counts compared to the control positive group, demonstrating anti-leukemic effects. G4 showed a slightly lower blast cell count than G3, suggesting Ashwagandha alone may have a marginally stronger effect. Both treatments are promising for managing leukemia.

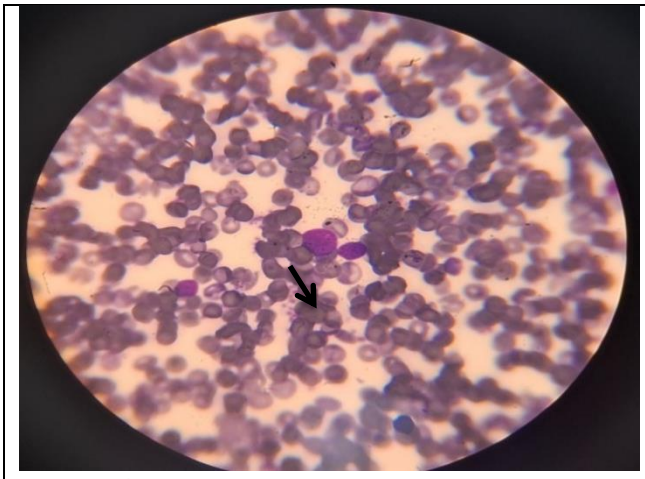


Figure 4.7 Blast cell microscopy

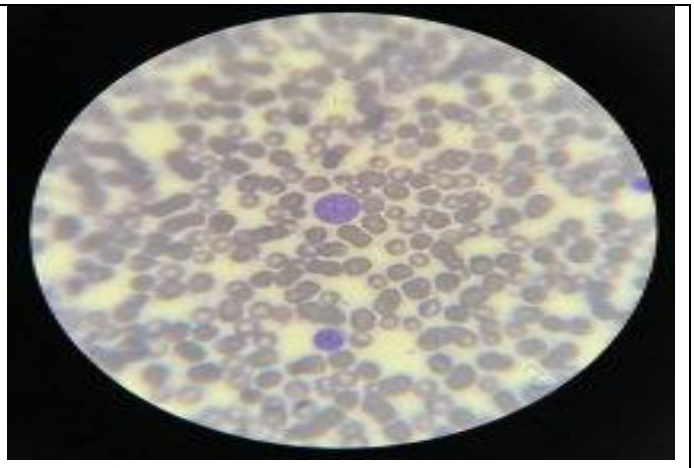


Figure 4.8 Blast cell microscopy

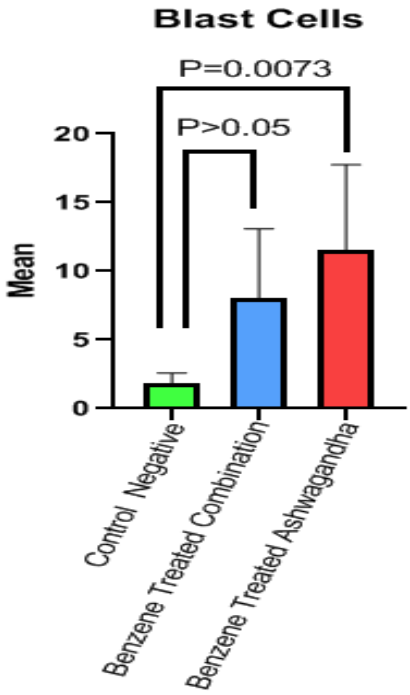


Figure 4.9 Shows blast cells mean and statistical analysis

Blast Cells (0-20%)		
Group	**Mean**	**P value**
Control Positive	23,50±1.607	<0.0001
Control Negative	1.833±0.3073	
Benzene Treated Combination	8.000±2.082	
Benzene Treated Ashwagandha	6.253±2.553	

Table 4.7 Shown blast cells counts in different study groups

4.1.8 RBCs

Both the Benzene Treated Combination Group and the Benzene Treated Ashwagandha Group maintained normal RBC counts. However, the combination treatment showed slightly higher RBC levels compared to Ashwagandha alone, suggesting it may better support red blood cell health and oxygen transport.

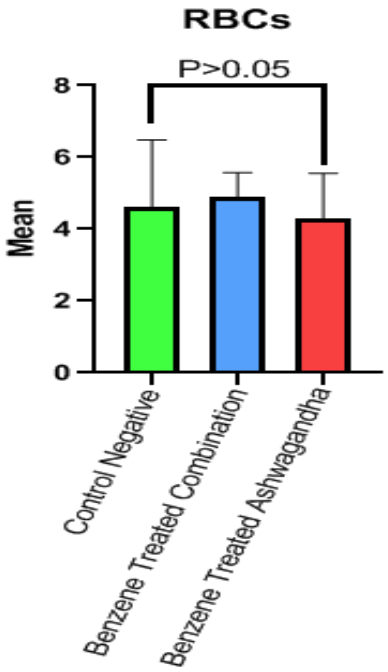


Figure 4.10 shows RBC means

RBCs (3.8-6.68 $10\times^{6}$ µL)		
Group	**Mean**	**P value**
Control Positive	4.872±0.3569	>0.05
Control Negative	4.617±0.7616	
Benzene Treated Combination	4.913±0.2710	
Benzene Treated Ashwagandha	4.287±0.5185	

Table 4.8 Exhibited RBC counts in all study groups.

4.1.9 Hemoglobin

G3 (combination) and G4 (Ashwagandha) showed slightly lower hemoglobin levels, with G4 being marginally lower. The combination treatment maintained levels closer to normal, suggesting it may better preserve oxygen-carrying capacity compared to Ashwagandha alone.

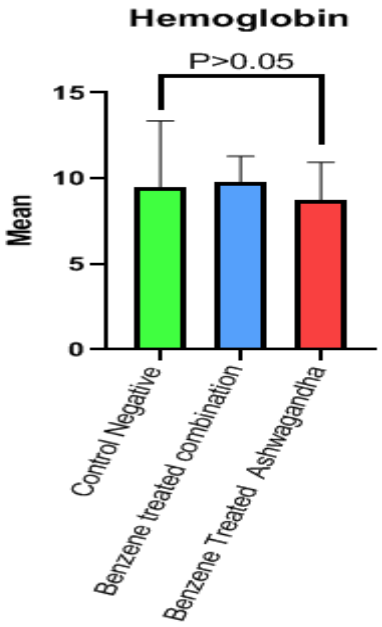


Figure 4.11 Hemoglobin statistical analysis

Hemoglobin (10.4-16.5(g/dl))		
Group	**Mean**	**P value**
Control Positive	9.717±0.4715	>0.05
Control Negative	9.5±1.573	
Benzene Treated Combination	9.800±0.6110	
Benzene Treated Ashwagandha	8.717±0.9046	

Table 4.9 Shown hemoglobin levels in study groups.

4.1.10 HCT

Both groups maintained normal HCT levels, but the combination treatment showed a more consistent and balanced effect, resembling the control group. Ashwagandha alone resulted in a slight HCT reduction, indicating a milder impact. Overall, the combination treatment better stabilizes hematocrit levels compared to Ashwagandha alone.

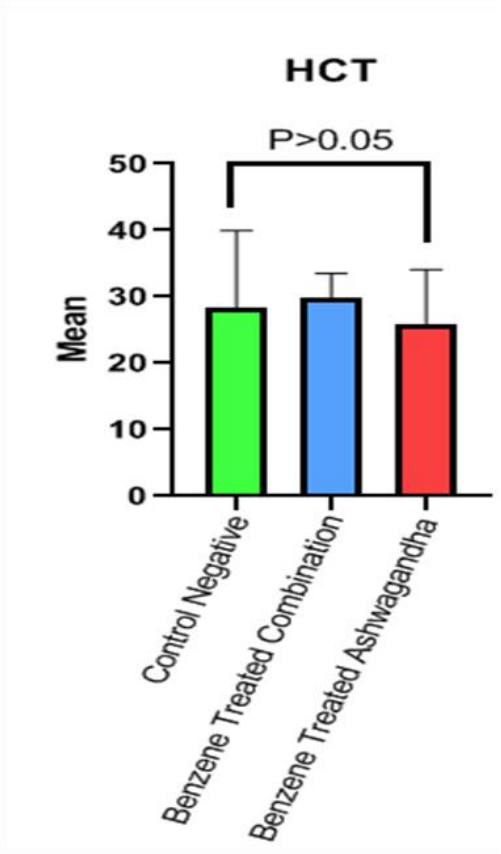
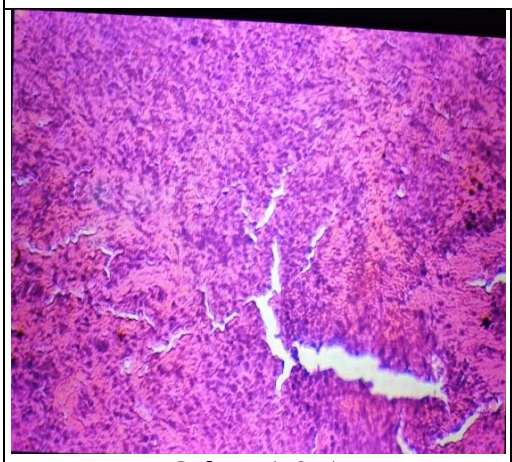
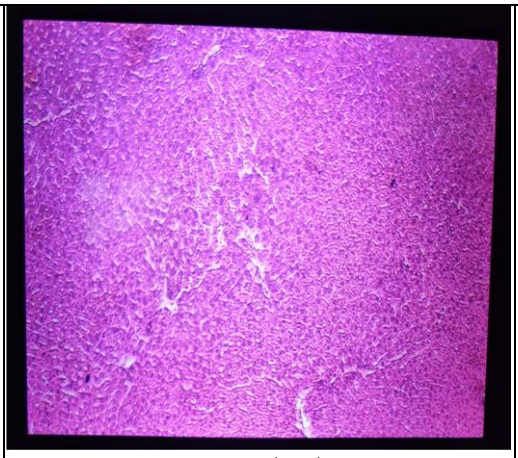
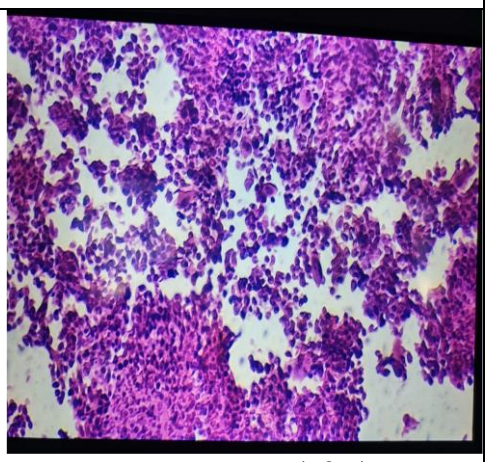


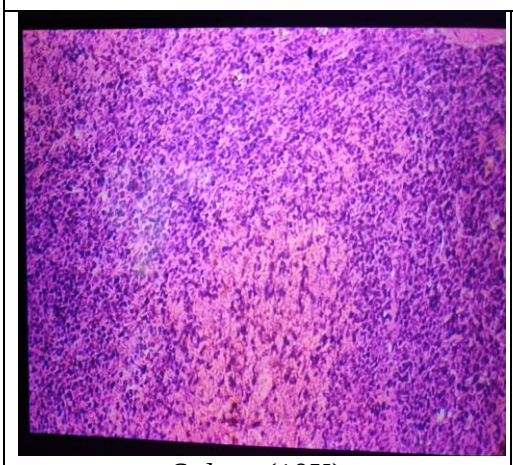
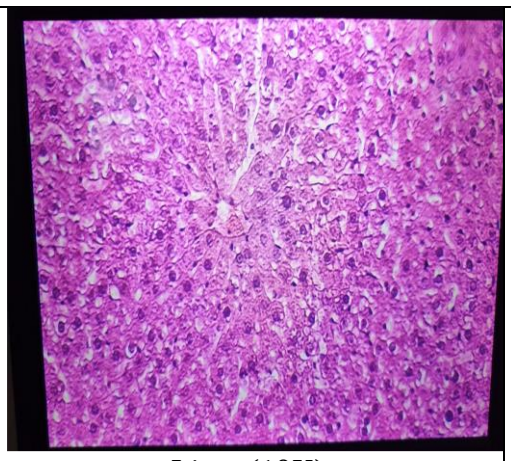
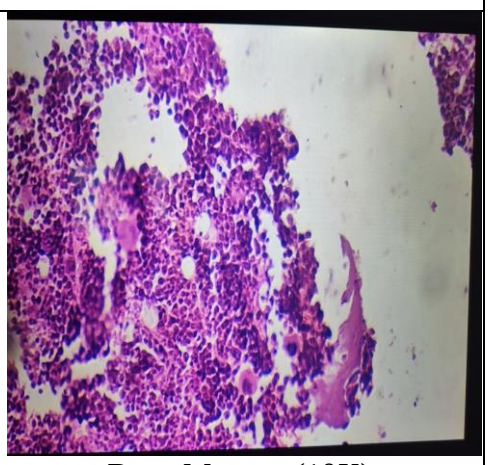
Figure 4.10 Showing HCT means and statistical analysis

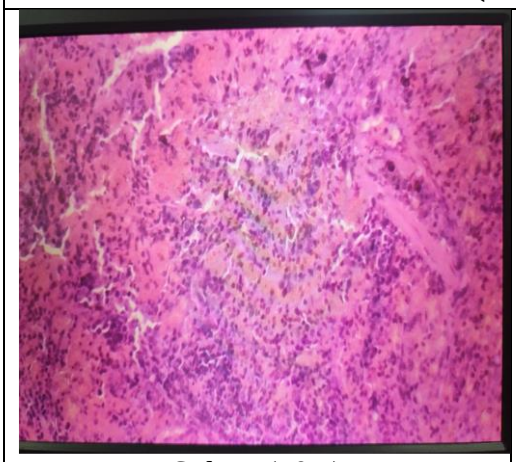
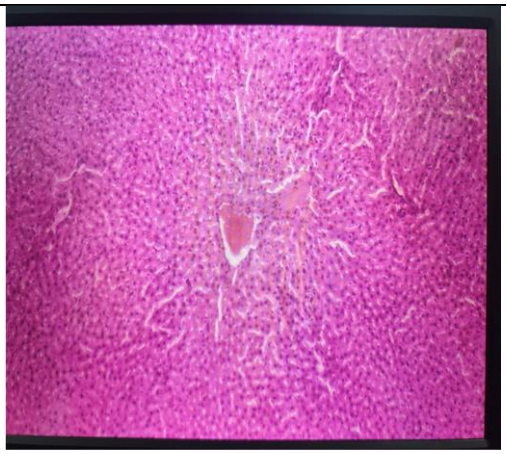
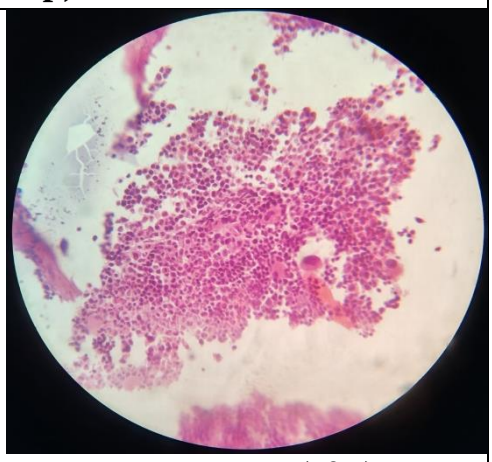
HCT 18-48(%)		
Group	**Mean**	**P value**
Control Positive	30.22±1.526	>0.05
Control Negative	28.30±4.743	
Benzene Treated Combination	29.82±1.519	
Benzene Treated Ashwagandha	25.98±3.290	

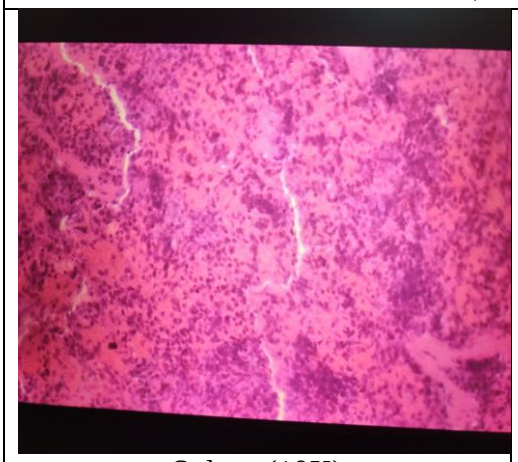
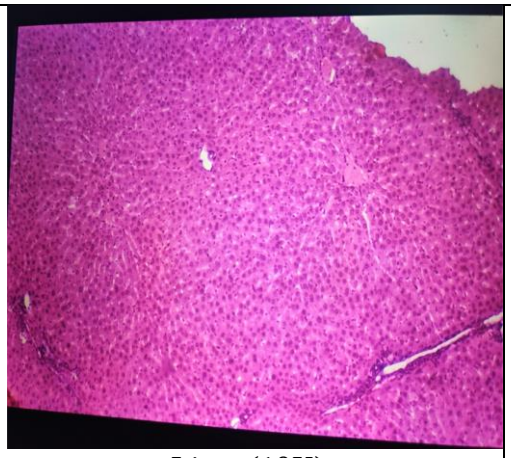
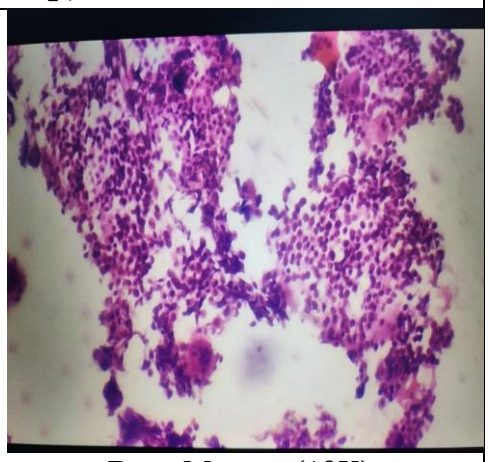
Table 4.10 Exhibited HCT percentage in all study groups

4.2 Histological Studies

G1 (Control Positive)		
		
Spleen (10X)	Liver (4X)	Bone Marrow (10X)
Figure 4.11: Sections showed destruction of the normal splenic morphology with secondary follicles formation associated with splenic cords congestion, hemosiderin deposition, prominent histiocytes in the red pulp, dilation of sinuses, hemorrhage and degeneration**.**	**Figure 4.12**: Sections showed mild mixed inflammatory cells infiltration predominantly lymphocytes in the portal tract with interface hepatitis associated with mild vascular congestion, mild focal fibrosis and mild fatty change (degenerative changes).	**Figure 4.13**: Sections showed marrow cellularity is approximately 80% which showed mild hyperplasia of all hematopoietic elements (including erythroid, granulocytic - monocytic and megakaryocytic series) with mild lymphoid cells hyperplasia and foci of degeneration.

G2 (Control Negative)		
		
Spleen (10X)	Liver (10X)	Bone Marrow (10X)
Figure 4.14: Sections showed normal morphology of splenic cords, sinusoids, red pulp, white pulp with normal lymphoid cells distribution**.**	**Figure 4.15**: Sections showed normal arrangement of hepatocytes, central hepatic venule and portal tract with mild vascular congestion.	**Figure 4.16**: Sections showed marrow cellularity is approximately 60-65% which showed all active normal hematopoietic elements (including erythroid, granulocytic-monocytic and megakaryocytic series).

G3 (Benzene Treated Combination Group)		
		
Spleen (10X)	Liver (10X)	Bone Marrow (10X)
Figure 4.17: Sections showed few histiocytes in the red pulp, few hemosiderin deposition ,dilation of sinuses, hemorrhage and degeneration (treatment reparative effect).	**Figure 4.18**: Sections showed mild mixed inflammatory cells infiltration predominantly lymphocytes in the portal tract with interface hepatitis associated with mild vascular congestion (treatment reparative effect).	**Figure 4.19**: Sections showed marrow cellularity is approximately 65% which showed all active normal hematopoietic elements (including erythroid, granulocytic-monocytic and megakaryocytic series) (treatment reparative effect).

G4 (Benzene Treated Ashwagandha Group)		
		
Spleen (10X)	Liver (10X)	Bone Marrow (10X)
Figure 4.20: Sections showed few splenic cords congestion, few hemosiderin deposition, histiocytes in the red pulp, mild focal dilation of sinuses (treatment reparative effect).	**Figure 4.21:** Sections showed few mixed inflammatory cells infiltration predominantly lymphocytes in the portal tract with mild vascular congestion (treatment reparative effect).	**Figure 4.22:** Sections showed marrow cellularity is approximately 70% which showed all active hematopoietic elements with mild hyperplasia of (erythroid, granulocytic-monocytic and megakaryocytic series) (treatment reparative effect).

CHAPTER FIVE
5.0 Discussion

In this study benzene, a known leukemia inducer was utilized to induce leukemia in male albino rats, which were treated with herbal supplements (Green Tea, Curcumin, Ashwagandha) following that, hematological parameters were studied in addition to histological studies. In the study findings, WBC levels for both treatment groups (benzene treated combination- benzene treated ashwagandha) had elevated levels when compared to control negative group however, the elevation was within normal range.

The mentioned study (168) administrated (Green tea, Curcumin) supplements to rats and found total WBCs levels at (10.08±0.80), in the current study, combination group received (Green tea, Curcumin) supplements with the addition of ashwagandha supplement , the result found was (10.57±1.92), both studies results show normal levels of total WBC when compared to control negative groups. Another study (190) held in rats showed total WBC levels of (7.62±0.16) however, in current study the level was slightly higher (10.57±1.92) in benzene treated ashwagandha group. A study (191) had WBC levels of (6.350 ± 0.3547), while in this study it was (10.47±0.6215) showing disagreeing on the average total WBCs counts in combination group.

In this study all groups had similar range of RBCs level when compared to control negative, additionally the same study (190) had RBCs level of (3.790 ± 0.0327), while in the held study RBCs level of (4.287±0.5185) was found showing similar results of RBCs in benzene treated ashwagnadha group . In the study (192) results showed RBCs levels of (4.60±0.16) and hemoglobin levels of (12.99±0.366) however, in current study Ashwagandha and curcumin were added to the group and the results were (4.913±0.2710) for RBCs and (9.800±0.6110) for hemoglobin showing that both studies had normal levels of RBCs and hemoglobin levels in combination group. Similarly a study used ashwagandha extract (193) was shown hemoglobin levels of (10.4±0.2 7), while in this study it was (8.717±0.904) showing favorable effects on RBCs levels in benzene treated ashwagandha group.

HCT levels were closely related to each other of both treatment groups when compared with control negative group, as in (194) showed HCT level of (25.60±0.49) while in current study it was (25.98±3.290) for ashwgandha group and (29.82±1.519) for combination group, both studies and in treatments used exhibited similar range of HCT counts showing stabilizing effects on HCT levels. A study (195) administrated curcumin based diet for the rats, the result was shown with higher HCT levels of (48.2±0.7) which is considerably higher than the result in this study (29.82±1.519) for combination group showing a disagreeing on HCT levels of the current and the mentioned studies. Neutrophil levels in current study can be notably be seen that treatment groups had higher neutrophil percentage than control negative group however, eosinophil was higher in control negative group than treatment groups.

A study (196) showed neutrophil counts of (30.00± 1.87%) and (1.60± 0.54) eosinophil level while, in this study curcumin and green tea extracts were given but

with an addition of ashwagandha supplement exhibited (34.70±4.137%) neutrophil level and (0.2333±0.04216%) eosinophil levels. Both studies showed similar results, indicating neutrophil regulating effects. Another study (197) results showed (31.00 ± 14.14%) neutrophil counts and (2.07 ± 1.98%) eosinophil counts with (31.87±4.779) and (0.6000±0.2944) neutrophil and eosinophil counts respectively in the current study showing similar results.

In the study (198) green tea and curcumin were given in the rat diet as individual groups, results were shown of green tea group (59.2±6.76) and (62.76±4.763) curcumin group for lymphocytes, and (5.167±0.752) with (5.717±1.036) for monocytes ,while in the current study, the results were (for combination group) (56.75±4.683) lymphocytes and (4.817±1.260) monocytes. All studies groups showed similar results indicating regulatory effects of the supplements used. In the current held study benzene treated ashwagandha group exhibited lymphocytes result of (45.32±12.14) and monocytes level of (6.683±0.4868), in (193) it was (86.4±0.41) and in (199) (4.00 ± 3.95) of lymphocytes and monocytes respectively. There is a high variation in lymphocytes findings among the mentioned study and the current held study, showing a notable disagreeing on the findings of the studies.

Treatment groups had lower than expected levels of blast cells when compared to control negative, indicating effectiveness of the supplements, notably both groups had similar results with no major/significant difference in blast cells count. The study (199) had blast cells count of 31%, chloroform treated group had 19% blast cells count however, in this study blast cells counts for combination and ashwagandha treated groups were (8.000±2.082) and (6.253±2.553) respectively, showing more potent effect than the treatment used in the mentioned study.

Conclusion

Ashwagandha (300 mg/kg) demonstrated anti-leukemic effects, particularly when combined with curcumin (200 mg/kg) and green tea (250 mg/kg), suggesting a potential synergistic therapeutic benefit.

Both benzene-treated groups exhibited similar hematological results in most parameters. However, the benzene-treated combination group (ashwagandha, curcumin, and green tea at 200 mg/kg, 200 mg/kg, and 250 mg/kg) exhibited higher lymphocyte levels and lower monocyte levels compared to the benzene-treated ashwagandha group, indicating a better prognosis for the combination therapy.

The benzene-treated ashwagandha group (300 mg/kg) exhibited improved histological features in the liver, spleen, and bone marrow, suggesting enhanced protection for these organs. The bone marrow displayed slightly higher cellularity, while liver sections showed reduced inflammatory cell infiltration, indicating a potential protective effect against benzene-induced toxicity.

Recommendations

1. Further studies with larger sample sizes and longer durations are needed to confirm the anti-leukemic effects of ashwagandha, curcumin, and green tea.
2. Investigating different dosages and treatment durations can help optimize their therapeutic potential

3. Research should explore the molecular and cellular mechanisms involved, particularly in apoptosis and immune response

4. Comparing this combination with conventional leukemia treatments could determine its potential as a complementary therapy.

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الملخص

الهدف

مادة البنزين يُعتبر .مختلفة عوامل نتيجة الناضجة غير البيضاء الدم خلايا بتكاثر تتميز حالة اللوكيميا تُعدّ .معينين وزمن بكمية لها التعرض عند اللوكيميا تطور إلى تؤدي أن يمكن كيميائية

المنهجية

الحقن طريق عن البالغة البيضاء الجرذان ذكور في اللوكيميا لتحفيز النقي البنزين استخدام تم ،الدراسة هذه في تقسيم تم ،اللوكيميا تحفيز بعد .يومين كل حقنة بمعدل أسابيع 3 لمدة كروماسولف بنزين لمحلول الوريدي تغذية أنبوب باستخدام الفم طريق عن إعطاؤها وتم ،(مجموعة لكل جرذان 6) مجموعات ثلاث إلى الجرذان (الكركمين ،الأخضر الشاي ،الأشواغاندا) من (كغم/ملغم 200 ،كغم/ملغم 250 ،كغم/ملغم 200) بجرعات من (كغم/ملغم 300) جرعة أخرى علاجية مجموعة إعطاء تم كما .متواصل شهر لمدة تركيبي كعلاج تحليل تم .القلب من مباشرة الدم عينات سحب بعد الجرذان تشريح تم ،العلاج فترة بعد .فردي كعلاج الأشواغاندا .وتقييمها التشريح بعد (والكبد ،الطحال ،العظم لنخاع) والنسيجية الدموية المعايير

النتائج

العلاج أن ورغم .السلبية بالمجموعة مقارنة البيضاء الدم خلايا عدد إجمالي في كبيرة زيادة العلاجات أظهرت الأشواغاندا أن إلى يشير مما ،طفيفًا كان الفرق أن إلا ،البيضاء الدم خلايا عدد في طفيفة زيادة عن أسفر المركب العلاج مجموعتي كلا في الحمراء الدم خلايا أعداد تحسنت ،كذلك .المناعي النشاط تعزيز في أيضًا فعالة وحدها .فعال بشكل الحمراء الدم خلايا مستويات العلاجات كلا دعمت حيث ،السلبية بالمجموعة مقارنة

من طبيعية مستويات العلاج مجموعات جميع أظهرت .اللوكيميا نشاط لتقييم الأرومية الخلايا أعداد استخدام تم يشير مما ،الأرومية الخلايا عدد حيث من الأقل المركبة بالتركيبة المعالجة المجموعة وكانت ،الأرومية الخلايا .فقط بالأشواغاندا المعالجة المجموعة من فعالية أكثر كانت التركيبة هذه أن إلى

المجموعة في حفظًا أفضل كانت الأنسجة بنية أن والكبد والطحال العظم لنخاع النسيجية الدراسات أظهرت نسيجية حالة وحدها الأشواغاندا تلقت التي المجموعة أظهرت ،ذلك ومع .السلبية بالمجموعة مقارنة المعالجة .المركبة بالتركيبة المعالجة بالمجموعة مقارنة أفضل

الاستنتاج

سواء البنزين سمية ضد وقائية وخصائص الدم لسرطان مضادة قوية بخصائص الأشواغاندا تتمتع ،عام بشكل العلاجات حققتها التي المعززة العلاجية الفوائد وتشير .الأخضر والشاي الكركمين مع بالتزامن أو فردي بشكل مستويات وزيادة ،الوحيدة الخلايا مستويات تقليل ذلك في بما ،تكاملي علاجي كخيار إمكاناتها إلى التركيبية 04:20.والطحال والكبد العظم نخاع في أكبر نسيجية حماية وتوفير ،اللمفاوية الخلايا

پێشەکی

.دەبن دروست جیاوازەوە هۆکاری بەهۆی کە دەناسرێتەوە خوێن سپیەکانی خڕۆکە زۆربوونی بە خوێن شێرپەنجەی
بڕێکی و ماوە لە کاتێک خوێن شێرپەنجەی گەشەکردنی هۆی ببێتە دەتوانێت کە کیمیاییە چارەسەرێکی بەنزین
.دەدرێت پێی دیاریکراودا

شێوازناسی

لە لێدان دەرزی بە ئەلیبنۆ پێگەیشتووی نێری جرجی لە خوێن شێرپەنجەی بە تووشبوون بۆ بەنزین ،توێژینەوەیەدا لەم
.ڕۆژ ٢ هەفتەیەك هەر لە بەکارهێنرا هەفتە ٣ ماوەی بۆ بەنزین دەمار
دەرخواردەدران دەمەوە ڕێگەی لە و (جرج 6 هەریەکەیان) گرووپ 3 بۆ کران دابەش جرجەکان ،خوێن شێرپەنجەی
وەک (زەردەچەوە ،سەوز چای ،ئەشواگاندا) (کگم/گرام ٢٠٠میلی/ ،کگم/گرام ٢٥٠میلی ،کگم/گرام ٢٠٠میلی) لەگەڵ
میلی ٣٠٠) بەکارهێنرا تەنیا بە ئەشواگاندا تر گرووپێکی .بەکارهێنران یەک لەسەر مانگ یەک ماوەی بۆ تێکەڵ گرووپێکی
دەرهێنانی بە خوێن نمونەی ئەوەی دوای کرا بۆ هەناویان توێکاری چارەسەری ماوەی پاش چارەسەر وەک (کگم/گرام
و ئەنجامدرا (جگەر – سپڵ – ئێسک مۆخی) توێژینەوەکانی هیستۆلۆجی و خوێن پێوەرەکانی .وەرگیراوە دڵەوە لە خوێن
.هەڵسەنگێنران توێکاری پاش

ئەنجامەکان

کۆنترۆڵی گرووپی بە بەراورد بە خوێنیان سپەکانی خڕۆکە ژمارەی بەرچاو شێوەیەکی بە چارەسەرەکە هەردوو
بەڵام ،لێکەوتەوە زیاتری کەمێک خوێنی سپیەکانی خڕۆکە ڕێژەی تێکەڵەکە چارەسەرە هەرچەندە .کرد زیاد نێگەتیڤ
،شێوە بەهەمان .بەرگری چالاکی بەهێزکردنی لە کاریگەرە بەتەنیا ئەشواگاندا کە دەریدەخات ،بوو کەم جیاوازییەکە
،نێگەتیڤ کۆنترۆڵی گرووپی بە بەراورد بە بوو باشتر چارەسەردا گرووپی هەردوو لە خوێن سورەکانی خڕۆکە ژمارەی
.دەکەن خوێن سوورەکانی خڕۆکە ئاستی لە پشتگیری کاریگەر شێوەیەکی بە چارەسەرەکە هەردوو ،ئەوەش سەرەڕای
ئاسایی ڕێژەی چارەسەر گرووپەکانی هەموو .بەکارهێنرا شێرپەنجە چالاکی هەڵسەنگاندنی بۆ تەقینەوە خانەکانی ژمارەی
نیشان ئەوە ،دا نیشان تەقینەوەیان خانەی ژمارەی کەمترین کە—تێکەڵ گرووپی .دا نیشان تەقینەوەیان خانەکانی ژمارەی
.ئەشواگاندا چارەسەرکراوی گرووپی لە بووە کاریگەرتر تێکەڵەیە ئەم کە دەدات

باشتر چارەسەرکراودا گرووپی لە شانە پێکهاتەی کە دەریخست جگەر و ئێسک،سپڵ مۆخی هیستۆلۆجی توێژینەوەکانی
بە وەردەگرن ئەشواگاندا پاشکۆی کە گرووپەی ئەو ،ئەوەشدا لەگەڵ .نێگەتیڤ کۆنترۆڵی گرووپی لە وەک پارێزراوە
دا نیشان باشتریان شانەی ،ئەنجامدراوە تێکەڵەیان چارەسەری کە گرووپەی ئەو لەگەڵ بەراورد

،بەکورتی:دەرئەنجام

دژی لە پاراستن و خوێن دژە بەهێزی تایبەتمەندی ئەشواگاندا
و زەردەچەوە لەگەڵ هاوبەشی بە هەم و تاک بە هەم بەنزین بوونی ژەهراوی
لەلایەن کراوە پێشنیار هاوکاری چارەسەری بژاردەی وەک ،سەوز چای
کەمبوونەوە لە بریتین کە تێکەڵ چارەسەری سوودەکانی
زیاتر هیستۆلۆجی و ،لیمفەخانە ئاستی بەرزبوونەوەی ،(خوێنە سپیەکانی خڕۆکە نمونەکانی لە یەکێك)مۆنۆسایت ئاستی
.دەکات سپڵ ئەندامەکانی و جگەر ،ئێسک مۆخی لە پارێزگاری