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Interlinking Human-Derived Leukemia Cells with Clinicopathological Therapeutics: Exploring Capsaicin's Anti-Cancer Mechanisms/potential for Leukemia Patients

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ABSTRACT

Capsaicin, a bioactive compound isolated from chilli peppers, comes out as a potential agent for its anti-proliferation role in leukemia patients' therapy. **Objectives:** This systematic review describes the Clinicopathological therapeutic potential of capsaicin against leukemia emphasizing the mechanism by which it inhibits growth through apoptosis, the cell cycle, and regulation of oncogenic signalling pathways in human-derived leukemia cell lines. **Methods:** According to PRISMA guidelines, the 75 studies were obtained from the various databases January 2013 and April 2024; Semantic Scholar, Google Scholar, PubMed as well as Frontiers and Link Springer. 50% (38) of the articles were taken from Semantic Scholar, 30% (22) from Google Scholar and 20% (15) from other search engines including PubMed and Link Springer. The papers included the inclusion criteria of PRISMA based on demographics, key outcomes and Anti-Cancer mechanisms majorly. **Results:** Capsaicin research published in America, Europe, Asia and Africa proves that it regulates vital processes at the cellular level including production of ROS, inhibition of NF-κB, STAT3, MAPK and cellular apoptosis. As human-derived cell lines are playing a pivotal role in cancer therapy, silicon methodologies along with in-vitro and in-vivo verification also shed more light on the improvement by capsaicin of the effectiveness of standard chemotherapeutic agents in combination with preferential killing of leukemic cells. **Conclusions:** Significantly, there were low levels of cytotoxicity of capsaicin to normal peripheral blood hematopoietic cells indicating that the compound is safe to use inhibiting the key oncogenic pathways and enhancing the efficacy of existing chemotherapeutic agents makes it a promising candidate for future therapeutic development.

INTRODUCTION

Leukemia is a hematological malignancy that starts in the marrow of the bones, leading to the uncontrolled spread of abnormal immunity-based blood cells which hinder the production of healthy blood cells. This condition is classified into different types, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [1, 2]. The global prevalence of leukemia varies, with higher values as seen in developed regions like North America and Europe, where the incidence can reach 8-10 cases per 100,000 individuals annually [3]. In contrast, Asia and Africa have lower incidence rates, although increasing industrialization and environmental changes have caused a slight rise in the number of cases [4]. The etiology of leukemia is multifactorial. Genetic problems such as mutations in tumour suppressor genes and oncogenes, chromosomal abnormalities like the Philadelphia chromosome t (9; 22) in CML, and defects in DNA repair mechanisms are well-established internal factors contributing to disease onset [5]. External factors, including exposure to ionizing radiation, chemicals like benzene, and infections caused by viruses such as the

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Epstein-Barr virus (EBV), also increase leukemia risk, particularly in individuals with pre-existing vulnerabilities [6, 7]. Region-specific causes vary across the world. In developed countries, leukemia is more frequently associated with environmental toxins and genetic factors, while in Asia, infections induced by viruses such as Human T-lymphotropic virus type 1 (HTLV-1) are more prevalent contributors [8]. In Europe, radiation exposure remains a significant risk factor, especially in regions affected by nuclear accidents like Chornobyl [9]. Unfortunately, the technology of these individualized treatments is not provided effectively to each patient, and patients in developing nations receiving initial-stage diagnosis and breakthrough treatment planning are excluded. Capsaicin has demonstrated anticancer properties by influencing pathways such as apoptosis, autophagy, and cell cycle arrest, making it a promising candidate for future therapies [10]. Knowledge of these risk factors is important for considering potential therapeutic strategies, for example, capsaicin – the substance responsible for the spiciness of chilli pepper. The present review has established that capsaicin has huge potential as an anticancer agent since it activates pathways that oppose the development of cancer such as apoptosis, autophagy as well as the cell cycle. It may reduce the risks linked with such risk factors through one or more processes. For instance, capsaicin can provoke apoptosis in leukemic cells due to oxidative stress and activation of pathways promoting pro-apoptosis and overcoming the benefits of genetic mutations and environmental carcinogens. Besides, inflammation is also considered a factor for cancer development, thus it could also work as an anti-inflammatory agent. The potential for capsaicin to enhance current chemotherapeutic regimens or act as a standalone treatment provides new hope for overcoming treatment resistance commonly observed in leukemia[11].

This study aims to establish how capsaicin targets and alters the activity of specific cancer-related genes, induces cell death and enhances the effectiveness of chemotherapeutic drugs in leukemia cells. The hypothesis is that the capsaicin through the transient receptor potential vanilloid 1 (TRPV1) receptor damages the mitochondria and triggers apoptosis in leukemia cells through the adenosine monophosphate-activated protein kinase and mechanistic target of rapamycin (AMPK/mTOR) pathway and other signaling pathways. The research will also assess its role in improving treatment outcomes and reducing chemotherapy-related toxicity. Knowing anti-cancer mechanisms is crucial when considering that substances like capsaicin can negatively influence cancer cell proliferation, promote cell death, and regulate pathways that are instrumental to cancer development. This work connects basic in vitro investigations of human-derived leukemia-derived cell lines (HL-60, K562, and Jurkat) to possible antineoplastic treatment strategies elucidated by the laboratory studies.

METHODS

The PRISMA guidelines for reporting were followed throughout the conduct of this study, which took place between January and August of 2024. It included 75 articles in English from the last 11 years (2013-2024). The papers included the following information, which was arranged systematically according to the inclusion criteria of PRISMA: author name followed by year, demographics, key outcomes, mechanisms, factors, study design, and references. The PRISMA guidelines were adopted to guide the systematic review of 75 articles used in the study. The inclusion criteria depended upon the essential features such as mechanism pathways, cell lines and outcomes peculiar to the investigations related to leukemia and capsaicin. To assess the potency of capsaicin in the various leukemia models, data analysis was directed to IC50 values together with cytotoxicity. Several search engines were used for the study; Semantic Scholar, PubMed and Google Scholar. 50% of the articles were taken from Semantic Scholar, 30% from Google Scholar and 20% from other search engines including PubMed. The search was conducted using phrases such as leukemia, capsaicin, cancer signalling pathways, cell lines anti-cancer activity etc. Article searches were done using keywords: Leukemia, capsaicin, NF-kb, STAT HL 60 etc. The articles which did not contain leukemia, and capsaicin as keywords and did not come under the range of years selected for study, did not meet the inclusion criteria and were eliminated in the filtering process. Inclusion criteria also focused on demographics and study design. 75 articles in total were downloaded from databases, 2 duplicates were removed and 73 were left for further study analysis. A total of 58 articles from the systematic review were eliminated out of 73 and 17 were left which were sorted and used (Figure 1).

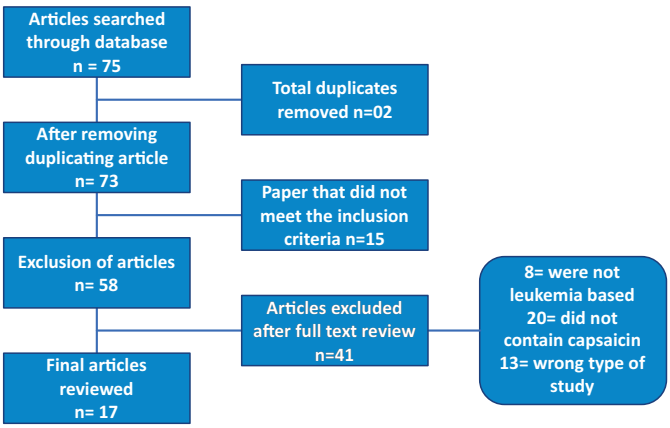

Figure 1: PRISMA Work Flow for Filtering Out Articles Focusing on Inclusion and Exclusion Method

RESULTS

The majority of papers were based on Acute Myeloid Leukemia and some were Chronic Myeloid Leukemia and

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Acute Lymphoblastic Leukemia. In this review, 47% of the articles belong to Asia, followed by Africa with 28%, and America and Europe both contribute 25% of the remaining. Out of 17 studies, 9 were taken from Semantic scholar, others were from various sources including Link Springer, Science Direct and Google Scholar [12]. 8 studies focused on Acute Myeloid Leukemia, 5 were focused on Chronic Myeloid Leukemia and 2 were focused on Acute Lymphoblastic Leukemia. Results of these studies [13-27, 28] are shown in the table 1.

Table 1: Systematic Review of Articles and Their Main Findings That Met the Inclusion Criteria of PRISMA

Reference (Location)	Study Design (Mechanism Pathway)	Cell line/ Human Model	Acute/ Chronic Leukemia	Results/ Findings	Conclusion
[13]	In silico and in-vitro (cell survival assay, microarray analysis)	K562 human cell line	Acute and chronic myeloid leukemia	14 out of 17 predicted pairs showing synergistic anticancer effects in cell survival assays.	The combination of capsaicin and mitoxantrone was highlighted for its significant anticancer synergy.
[14]	In vitro (lysosomal degradation)	Hsp 70	Chronic lymphocytic leukemia	Capsaicin promotes lysosomal degradation of Hsp70 and enhancing the anti-tumor effects.	Capsaicin can serve as a scaffold for developing novel Hsp90 and Hsp70 inhibitors. Acts as cancer co-therapeutic. This study demonstrates lysosomal degradation of Hsp70 by enhancing efficacy of chemotherapy.
[15]	In vitro (cell cytotoxicity)	CEM/CCRF, CEM/ADR5000	Acute myeloid leukemia	Capsaicin showed the highest cytotoxicity against p53 knockout HCT116 and CEM/CCRF leukemia cells. It showed reduced proliferation leukemia cells in a body.	Capsaicin is a potent anti-proliferative agent
[16]	In vitro (apoptosis, STAT3, NF-κB and cancer cell signalling pathway)	Jurkat cells	Jurkat cells	N-AVAM analogues induce apoptosis in leukemia cells, showing increased activity of caspase -8 and FADD, resulting in cancer cell death.	N-AVAM capsaicin analogues present promising potential for cancer therapy
[17]	In vitro (apoptosis)	K562 cells	Chronic Myeloid Leukemia	Capsaicin-loaded nanoliposomes showed significantly improved anticancer activity with lower IC50 values (17.88 μM) against leukemia cells	Capsaicin-loaded nanoliposomes enhance the anticancer effects of capsaicin by improving its bioavailability and selectivity for cancer cells
[18]	Invitro and Insilico (ROS generation)	CCRF-CEM, HL-60, K-562, MOLT-4, RPMI-8226, SR Cell lines	Acute and chronic myeloid leukemia	Capsaicin derivative 2a showed strong antiproliferative activity with 29.16% growth inhibition in MOLT-4 and 34.67% in CCRF -CEM leukemia cells.	The synthesized capsaicin analogues, particularly compound 20a, demonstrated significant anticancer activity.
[19]	In Vitro (JAK/STAT pathway)	K562 cells	Chronic myeloid leukemia	Capsaicin inhibited STAT3 expression. Downregulation of miR-520a-5p enhanced the inhibition of cell proliferation and increased apoptosis in K562 cells.	miR-520a-5p acts as an oncogene by targeting STAT3, and its inhibition, combined with cap saicin treatment, reduces leukemic cell viability and induces apoptosis.
[20]	Invitro (JAK-STAT signalling pathway, apoptosis)	HEL, THP1 cells	Acute myeloid leukemia and chronic myelogenous leukemia	Phytochemicals like capsaicin inhibited JAK-STAT pathway activation,reducing leukemia cell proliferation and inducing apoptosis	Phytochemicals, particularly those targeting STAT3, demonstrate potential in treating leukemia by disrupting the JAK-STAT pathway.

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[21]	In Vitro (MAPK signalling pathway)	JSC-1 cells	Acute lymphoblastic leukemia	Capsaicin-induced apoptosis via caspase -9 activation.	Capsaicin shows potential as a therapeutic agent for PEL by inhibiting ERK and p38 MAPK signaling pathways
[22]	In vitro (oxidative stress, and apoptosis)	K562, KU812, MOLM-6 cell lines	Chronic Myeloid Leukemia	Capsaicin worked synergistically when combined with imatinib to improve anticancer activity.	Capsaicin, in combination with imatinib, shows significant potential as a complementary treatment for chronic myeloid leukemia.
[23]	In Vitro (cell cycle progression , apoptosis)	Human KB cancer cells	General	Capsaicin inhibited the proliferation of KB cells,induced apoptosis, and led to cell cycle arrest at the G2/M phase.	Capsaicin modulates cell cycle progression and induces apoptosis through mitochondrial and caspase pathways in human cancer cells
[24]	In vitro (apoptosis and various cell signalling pathways)	HL-60 and HL-525 cell lines	Acute and chronic myeloid leukemia	Capsaicin induces apoptosis in leukemia cells through oxidative stress and activation of caspase pathways.	Capsaicin holds promise as an anticancer agent by targeting apoptosis pathways in leukemia cells, particularly through the generation of ROS and the activation of apoptotic signals.
[25]	In Vitro (apoptosis)	JSC-1 cell lines	Acute lymphoblastic leukemia	Capsaicin promotes apoptosis in leukemia cells by upregulating ATF4 protein levels	Capsaicin triggers the ATF4-CHOP-PUMA pathway to induce apoptosis in leukemia cells, suggesting its potential as a treatment option for leukemia
[26]	In Vitro (apoptosis induction, anti-inflammatory actions, and cell cycle regulation)	Human CML cell lines	Acute and chronic myeloid leukemia	Capsaicin can inhibit metastasis by modulating pathways such as VEGF,MMP9, AMPK-NF-kB, and p38 MAPK.	Capsaicin holds potential for preventing cancer metastasis by inhibiting critical pathways involved in angiogenesis, matrix degradation,and cell migration as in leukemia
[27]	In vitro (Apoptosis)	HL 60 cell line	Acute Myeloid Leukemia	Capsaicin effectively induces apoptosis in HL-60 cells by increasing Caspase-3 and Caspase-9. With an IC50 value of 16.7 µM.	Capsaicin demonstrated strong potential as a natural chemotherapeutic agent against leukemia, specifically through pro-apoptotic mechanisms.
[28]	In vivo and in vitro (tumour-induced Angiogenesis)	Human endothelial cells	N.A	Tumor-induced angiogenesis is directly related to blood cancer. Capsaicin inhibited VEGF-induced angiogenesis in cells in the chorioallantoic membrane of the chick model.	Capsaicin suppressed tumor -induced angiogenesis in the chick chorioallantoic membrane assay. Angiogenesis is linked with the spread of cancer through blood

DISCUSSION

Leukemia, as a systemic disease, is the result of multiple factors including genetics and environment in which malignant or cancerous cells with special-functional properties than normal cells proliferate and multiply out of control [29]. The reports also reveal that when a woman is pregnant, contracting the influenza virus through the use of antibiotics puts her and her fetus at a higher risk of acute lymphoid leukemia [30]. Infections are involved especially for acute lymphoblastic leukemia as shown in some mice models [31]. Epidemiological evidence indicates that smoking is the most substantial risk for leukemia mortality and morbidity, it has a more severe effect in males than in females, and body mass index also plays a pivotal role here [32]. Some of the relevant risk factors for developing AML include hepatitis C virus infection and a history of exposure to environmental factors that can be used as home

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decoration [33]. Leukemia is a malignancy of hematopoietic stem cells characterized by abnormal differentiation and proliferation [33]. Recent research has highlighted the complex interplay of various factors in leukemia pathogenesis. Natural killer (NK) cells, critical for cancer cell elimination, are being explored for immunotherapy, including adoptive transfer and CAR-NK approaches. Non-coding RNAs have emerged as potential diagnostic and prognostic biomarkers due to their involvement in oncogenic processes [34]. The transient receptor potential vanilloid 1 (TRPV1) receptors, which are essential for maintaining cellular homeostasis, are one of the primary mechanisms through which capsaicin performs its therapeutic job. When capsaicin binds to TRPV1, calcium enters the cell, causing mitochondrial malfunction, the production of reactive oxygen species (ROS), and the resulting activation of pro-apoptotic pathways [35]. This initiates the release of cytochrome c from the mitochondria, activating the caspase cascade, and leading to programmed cell death, which is essential for controlling malignant cell growth [36]. Furthermore, it has been demonstrated that capsaicin affects several important transcription factors, including NF-κB, STAT3, and p53, which frequently get abnormal in leukemia cells and are implicated in the development of leukemia. Capsaicin increases the effectiveness of traditional chemotherapy by inhibiting NF-κB activity, which makes leukemia cells more susceptible to apoptosis [37]. Moreover, capsaicin enhances the expression of p53, a well-known tumor suppressor, facilitating the repair of damaged DNA and inducing cell cycle arrest [38]. Capsaicin's ability to induce autophagy, a cellular breakdown process, demonstrates its therapeutic value. In cancer, autophagy serves as a trigger for some cancer-related cell death events as well as a survival strategy for cancer cells undergoing stress. It has been demonstrated that capsaicin causes apoptotic cell death in leukemia via altering the AMPK/mTOR signalling pathway, which controls autophagy and cellular metabolism. [39]. It is observed that capsaicin triggers autophagy in different types of human cancer cells such as oral squamous cell carcinoma and renal cell carcinoma. This autophagy induction occurs through several signaling pathways such as TFEB, AMPK/mTOR and ULK1. Capsaicin possesses anticancer effects in the following ways: anti-inflammatory, antioxidant, and anti-mutagenic. It is involved in the regulation of apoptosis, angiogenesis, and cell division; modulating signalling networks like PI3K/AKT and NF-κB. Capsaicin regulates TRPV1 receptors which leads to the release of calcium, disruption of mitochondrial membrane, and induce production of ROS that cause apoptosis. A study showed that capsaicin caused apoptosis through the AMPK/mTOR signalling pathway. Despite its promising anticancer effects, the therapeutic application of capsaicin in leukemia has certain limitations. The concentration of capsaicin required to induce apoptosis in cancer cells can sometimes cause cytotoxicity in normal cells, raising concerns about its safety and potential side effects in clinical settings [40]. Furthermore, the bioavailability of capsaicin is relatively low, as it is rapidly metabolized in the liver, which limits its effectiveness when administered orally [41]. These limitations necessitate further research into optimizing capsaicin formulations, such as using nanoparticles or liposomes to enhance its delivery and reduce off-target effects [42]. The experiments carried out on cultures and animals prove the hypothesis that capsaicin has a pro-apoptotic effect and increases the chemotherapy efficacy in leukemia therapy. Investigation revealed that capsaicin inhibits cell proliferation and causes apoptosis in various Human leukemia cell lines including HL-60 K, 562, and Jurkat cells through caspase 9 activation with downregulation of anti-apoptotic oncogenic signal transduction Pathways including AMPK/mTOR. The above cellular effects were substantiated in in-vivo models where treatment with capsaicin caused a massive decrease in tumour volume ranging from 20-40 % and this was due to the density of the pro-apoptotic and anti-proliferative effects of the compound. Further, the present study revealed that capsaicin can potentiate normal chemotherapeutic drugs including mitoxantrone and cause increased tumour regression in vivo. Combined cellular and organism-level findings suggest that capsaicin acts as an independent chemotherapeutic agent; it also boosts the effects of traditional chemotherapy drugs and may be useful for leukaemia types that are resistant to conventional treatments. These results have the potential to improve chemotherapy efficacy by increasing the biological effects of the usual chemotherapeutic drugs and decreasing the toxicity as well. For instance, there is evidence that capsaicin enhances the sensitivity of leukemia cells to such drugs as doxorubicin and vincristine thus making it possible to use small doses of these products for similar desired effects. This is attained by its capacity to bring about apoptosis and disarm significant revival circuits in the malignant growth cells hence making them vulnerable to chemo treatments. Also, the synergy between capsaicin and other agents like imatinib has been

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found to boost antitumor effects through multiple pathways as well as to overcome the resistance that is a particular issue in cancer therapies, in particular, leukemia. Although the systemic bioavailability of capsaicin is low because of first-pass metabolism, future endeavors require long-term studies for the enhancement of delivering capsaicin to maximize its pharmacological effects. Some of the concrete strategies may be liposome formulation, nanoparticles or solid lipid nanoparticles as the solubility and stabilization of capsaicin can be an issue [43]. Nonetheless, future works which involve observing the enhancement of the co-administration with absorption enhancers or the development of transdermal delivery systems will improve the bioavailability. Since these strategies are based on a synthesis of capsaicin and its delivery to the target therapeutic site, clinical trials testing these approaches will be necessary to identify the most effective ways of delivering it therapeutically [44].

CONCLUSIONS

It was concluded that capsaicin exhibits promising anticancer activity, yet the following gaps need to be filled. Future work should analyze the safety of capsaicin in the Leukemia patient profile and its bioavailability, and toxicity when administered at therapeutic concentrations. Specific experimental procedures should be in vitro and animal studies to assess capsaicin's interaction with the baseline chemotherapy protocols. Further, there is a need to conduct clinical trials to determine the effectiveness of advanced formulation of capsaicin in enhancing the clinical results in the leukemia management. Closely evaluating these gaps will be quintessential in the provision of further understanding of the role of capsaicin as adjuvant therapy in hematological malignancy.

Authors Contribution

Conceptualization: MM, FC, AK
Methodology: MM, FC, AK
Formal analysis: MM, FC, AK
Writing review and editing: ATN, JA, SK, DD

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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