Clinical study of curcumin on different stages of leukemia:
An overview

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Abstract: Curcumin is a polyphenol originated from curcuma longa of ginger family, Zingiberaceae. Which is used as spice and herbal medicine. It has various medicinal properties like anti-cancer, anti-inflammatory, and helps in maintain the optimum cholesterol, weight and skin care. According to some research, the cancer causing agents and then treated with curcumin didn’t develop stomach, colon and skin cancer. Majority of the chemotherapeutic agents not kill only tumour cells, but also the normal cells and cost of the treatment very high. And the next part is the Inflammation might also occurs in various diseases like cancer, allergy, asthma, diabetes, and heart diseases and also found in various arthritis like Rheumatoid, psoriatic, and Gouty arthritis. And the major cause for the Inflammation oxidative stress. SoUsing of various synthetic agents in treatment of inflammatory diseases and cancer, might cause various side effects in majority of the population. Most serious diseases in the world right now is leukemia, which defines increased number of blood cells. By in this review article, which aims to give various uses and actions of curcumin against different modes of leukemia.

Keywords: Curcumin, Leukemia, Stages, Effects.
1. INTRODUCTION

Whether the drugs found today are effective, productive, and inexpensive than generic medicinal products, which patent expired at the end or the medicinal products which decades old could be answered no to most of the modern medicines. If so revisiting and reviving this rational product is essential for human health. So curcumin is natural spice, in which its history goes over five thousand years ago (5000) in the Ayurveda medicine (means long life). Its extracted from the plant of *curcuma longa* of the family of zingiberaceae (Gopi et al., 2017). The rhizomes of the plant used as a spice and it’s been used as a medicinal products by the Indian subcontinent people’s for centuries with no acknowledged side effects. Turmeric is looks like golden colour and it’s used as a culinary spice in Indian subcontinent. Turmeric is named as Indian saffron in Europe, because of its natural obtained colour and the taste. Turmeric is named as an haldi in India. India is the primary exporter of Turmeric to world. Turmeric has an antioxidant property that mechanism helps in preservation of foods. In Indian and Chinese medicines turmericis used as a anti-inflammatory agents for chest pain, menstrual difficulties, gastric, colic and toothaches. Also this herb used as a cosmetic and assist in curing wounds, scars and liver issues (Aggarwal et al., 2013).

Recent studies and discoveries on the natural medicine apart from allopathy medicines has gave attention to the ancient medicines. Recent studies and researches on turmeric, which shows that it have wide variety of beneficial effects to the human like, chemotherapeutic, preventive, antioxidant, anti-inflammatory activities (Hatcher et al., 2008). Another type and the most serious part of cancer is blood cancer or leukemia. Which acute and chronic disease, seems in blood. Leukemia is Characterized as an greater number or gradually increasing of white blood cells in the bone marrow. Major classification of leukemia is Acute and chronic. And further classified into Acute myeloid leukemia, Acute lymphoblastic leukemia, chronic myeloid leukemia, chronic lymphoblastic leukemia (Xiao et al., 1997). This type made several genetic changes in the cells and cause or lead to death. There several methods and treatments has arrived for the leukemia, but the natural medicine like curcumin has major clinical effects on different types of leukemia, which is also clinically proven many researches (Jabbour & Kantarjian, 2016).
2. CHEMICAL PROPERTIES

The active ingredient of curcumin which having a \([1, \text{ 7-bis (hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione}]\), which shows an therapeutic activity in various conditions (Salem, Rohani & Gillies, 2014). Curcumin is an ingredient from the turmeric and has a structure of (bis- a, b-unsaturated b-diketone). It shows that curcumin has less solubility in water and good solubility with fats, ethanol. Using an steam distillation various essential oils can be extracted from the rhizomes like phellandrene, sabinene, borneol, sesquiterpene, zingiberene. At the structural level curcumin encourages the equilibrium enol tautomer and bis ketomer (Huang & Beaver’s, 2011). This molecular structure dominates acidic and neutral aqueous liquids. Due to its two keto forms in the methoxy phenol which dominates in the cell membrane also.
Curcumin has a high potent activity at pH; 3-7 due to an H-atom donor. Naturally curcumin has an ketone group, the hepatodienone bond, which having a two methoxyphenol rings with highly active carbon atom. On the adjacent sides of oxygen carbon is very weak in nature, due to delocalisation of unpaired electron. At the pH 8 curcumin act as an electron donor due to an enolate group (Mohamed, El-Shishtawy, Al-Bar & Al-Najada, 2016). Curcumin is usually not stable in basic pH and might change to different forms of substances like ferulic acid vanillin, diferuloylmethane. At acidic pH the degradation is very slower than basic pH. The molecular weight of curcumin is 368.68 g/mol and melting point is 183°C. The absorption of curcumin is 420 nm, while checking the absorption (Sharma et al., 2005).

3. LEUKEMIA
Leukaemia is a condition in which the white blood cells affected by cancer. Lymphocytes and granulocytes are the white blood cells which are mainly affected by cancer and and the condition is known as Leukaemia. Lymphocytic leukemia arise from cancerous lymphocytes. Cancerous granulocytes causes a myleoid or myelogenous leukemia ("Leukemia - Diagnosis and treatment - Mayo Clinic", 2021). This condition might affect in two different ways like Acute or chronic. According to this classification the leukaemia is divided into four types ("Types of Leukemia: Common, Rare and More Varieties", 2021).

- Acute myeloid leukemia
- Chronic myeloid leukemia
- Acute lymphoblastic leukemia
- Chronic lymphoblastic leukemia

3.1. Stages and types of leukemia:

<table>
<thead>
<tr>
<th>Fab type</th>
<th>Name</th>
<th>% of adult AML patients</th>
<th>Prognosis compared to average for AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated acute myeloblastic</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukaemia with minimal maturation</td>
<td>15%</td>
<td>Average</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukaemia with maturation</td>
<td>25%</td>
<td>Better</td>
</tr>
</tbody>
</table>
3.2. **Acute myeloid leukemia:** Acute myeloid leukemia (AML) is a disorder, with association with improper growth of myeloid cells in bone marrow and peripheral blood. A few years ago the disease was incurable, but in recent years it is curable even lesser 60 years old people.

Lymphoblasts are abnormal blood forming cells, where they replicate automatically, with forming an normal blood cells. Morphological the lymphocyte is lesser in size, when compared to AML blasts. This condition is known as acute myeloid leukemia (Hussain et al., 2006). AML is a most common type of leukemia which mainly affects an children.

3.3. **Stages of chronic myeloid leukemia:**

Generally chronic myeloid leukemia occurs three types chronic, accelerated, blast types.

3.3.1. **Chronic phase:** This type of phases of phase occurs, when non treatment of diseases for long time. Blood and bone marrow contain less than 10% of blasts, which are non-proper grown WBC(white blood cells).(COVID-19) et al., 2021).When improper treatment on Chronic myeloid leukemia , which lead to accelerated and blast phase ,seems in 90% of people.

<table>
<thead>
<tr>
<th></th>
<th>Acute promyelocytic leukaemia</th>
<th>10%</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukaemia</td>
<td>20%</td>
<td>Average</td>
</tr>
<tr>
<td>M4 eos</td>
<td>Acute myelomonocytic leukaemia with eosinophilia</td>
<td>5%</td>
<td>Better</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukaemia</td>
<td>10%</td>
<td>Average</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroid leukaemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukaemia</td>
<td>5%</td>
<td>Worse</td>
</tr>
</tbody>
</table>

**Table 1:** The French- American-British Classification. Note; Adapted from french-American-british classification by Ananya mandal, reviewed by April cashin garbutt.
3.3.2. Accelerated phase: Basically accelerated phase shows around 9 to 20% of blasts in the blood and bone marrow. Somewhere shows more than that in the basophils of white blood cells. This may occur due to the some cellular damage and mutations, DNA damage in the cells.

3.3.3. Blast phase: The final phase of chronic myeloid leukemia which preferably shows more than 21% of blasts in the bone and bone marrow often grown very highly in the white blood cells. Due to several genetic changes in the cells due the chronic myeloid leukemia, might results in initial symptoms like fever, enlarged spleen, and weight loss (Xiao, Hao & Bian, 1997).

3.4. Chronic myeloid leukemia: Chronic myeloid leukemia is an neoplastic disorder related bone marrow. CML is an myoproliferative disorder, with rapid growth of blood cells in bone marrow. This condition is occurred by an Philadelphia chromosome occurred by an single hematopoietic stem cells. The effect of CML is 1-2 people’s in 100,000 population. Where mostly seems in median age between 40 to 65 years old. Males are more affected than females (Jabbour, 2015).

3.5. Acute lymphoblastic leukemia (ALL): Acute lymphoblastic leukemia is condition of which that affects mainly an lymphoid progenitor cells in the bone and blood and interstitial sites. Acute lymphoblastic leukemia affects most probably in children. The some survey shown that 80% percent ALL cases are seen in childrens. The pathogenesis of ALL (Acute lymphoblastic leukemia) shows irregular proliferation and division of a clonal of lymphoid cells.

3.6. Stages of chronic lymphoblastic leukemia: The most often used system of classification is Rai system of chronic lymphoblastic leukemia. This system mainly comprised of five stages from 0 to IV. The stages like stage 0 which (less)risk, stage I and II is (intermediate), Stage III and IV(High risk) (“Chronic Lymphocytic Leukemia Stages”, 2021).

3.6.1. Stage 0: This stages means the larger number of white blood cells is also known as lymphocytosis. Compared to other this stage CLL (Chronic lymphoblastic leukemia) has an longer survival rate.

3.6.2. Stage 1: In this stage it found that larger number of growth in lymphocytes in the blood. Lymph nodes are larger than usual. The counts of the red blood cells and platelets are close to normal.
3.6.3. Stage 2: In this stage, it found that larger number of lymphocytes in the blood. And results enlarged spleen (spleenomegaly) and enlarged liver (hepatomegaly). The blood counts are close to normal and have a medium risk.

3.6.4. Stage 3: In this stage, it seems very larger amount of lymphocytes in the blood. And leads to the anaemia (low Red blood cells count). The liver, spleen and lymph is larger than usual because of increasing cell count due to leukemia. This stage has an higher risk.

3.6.5. Stage 4: This stage also as same as stage 4, but the platelets count are leads to very low in percentage (thrombocytopenia). And have a higher risk of death (Shanafelt, 2017).

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical features</th>
<th>Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Lesser than three years of Lymphodenophathy; No possibility of anaemia and thrombocytopenia</td>
<td>Around 12 years</td>
</tr>
<tr>
<td>Stage B</td>
<td>More than three areas; lesser possibly of anaemia and thrombocytopenia</td>
<td>7 years</td>
</tr>
<tr>
<td>Stage C</td>
<td>Found lesser Haemoglobin content (HG&lt;100g/L) and lesser platelets count (&lt;100×10g/L)</td>
<td>2-4 year’s</td>
</tr>
</tbody>
</table>

3.7. Chronic lymphoblastic leukemia (CLL): The clonal development and aggregation of mature, normally CD5-positive B-cells in the blood, bone marrow, lymph nodes, and spleen are hallmarks of chronic lymphocytic leukemia. It was recently recorded that the ability to generate clonal B cells in CLL could be acquired at the hematopoietic stem cell (HSC) stage, meaning that the primary leukemogenic event in CLL could involve multipotent, self-renewing HSCs (“Chronic Lymphocytic Leukemia Stages”, 2021).
4. EFFECTS OF CURCUMIN IN VARIOUS STAGES OF LEUKEMIA

4.1. Acute myeloid leukemia: In both insensitive KG1a, Kasumi-1 and DNR-insensitive U937 cells, Curcumin inhibited cloning and induction of apoptosis and G1/s arrest. Induction of apoptosis with Curcumin is associated with Lower Bcl-2 RNA and protein interpretation, Matrix metalloproteinase (MMP) loss and caspase-3 activation followed by PARP-degradation (Padmanabhan, 2017). Anti-tumour activity of DNR in DNR-insensitive KG1a and Kasumi-1 cells, which is preceded by a reduction in Bcl-2 expression is increased due to the effect of curcumin. As a result, siRNA targeting Bcl-2 made KG1a and kasumi-1 cells, more susceptible to DNA-induced apoptosis. Curcumin inhibited expression level, selectively inhibited proliferation and therapeutically increased DNR cytotoxicity in primary CD34+ Acute myeloid leukemia cells. This cells susceptible to minor effectiveness in normal cells of CD34+ hematopoietic progenitors. As a result, DNR-insensitive CD34+ Acute myeloid leukaemia cells and primary CD34+ Acute myeloid leukemia cells, inhibited Bcl-2 induction of apoptosis (Martínez-Castillo et al., 2018).

4.2. Chronic myeloid leukemia: The myeloid cells like K562 and LAMA84 are treated with curcumin for the whole day. As a result treating with the curcumin shows inhibition of cell proliferation in CML (Chronic myeloid leukemia) (Jabbour & Kantarjian, 2016). The another effects of curcumin on chronic myeloid leukemia cells is that decreasing the miR-21 levels. Basically miR-21 has higher amount of exosomes, so these are released by an K562 and LAMA84 cells. After the treatment of curcumin and sphingomyelinase-2 inhibitor with this cells, shows an inhibited activity of exosomes in the cells of K562 and LAMA 84 (Jabbour, 2015). Cell migration is main reason for the spreading of tumour cells. So the effect of alone sphingomyelinase-2 inhibitor gives greater activity of migration of leukemia cells in bone marrow. Combination of curcumin and sphingomyelinase-2 inhibitor shows inhibition of leukemia cells (Martínez-Castillo et al., 2018).

4.3. Acute lymphoblastic leukemia: In Acute lymphoblastic leukemia the proliferation and apoptosis is inhibited and induced by the lowering the regulation of AKT-kinase signaling by the action of curcumin in sufficient amount. By less active signaling proceeds with activation of caspase-8 and BID truncation, which is preceded with loss of cytochrome c to the cytosol and mitochondrial membrane. Acute lymphoblastic leukemia cell death is decreased by induction of curcumin of the cyt-c leads to capase-9 and 3 activation and down regulate of the active proteins like survivin etc. Several research results shown that curcumin inhibit malignant cells of lymphoblastic leukemia (Haghighian et al., 2020).
4.4. **Chronic lymphoblastic leukemia:** Curcumin has inhibit several stages of neoplasm and there several methods and mechanism has been discovered using the Curcumin. Curcumin inhibit and induce proliferation and apoptosis of different cells chronic lymphoblastic leukemia by the inhibition of STAT3, AKT, and NF-kB which are active in Chronic lymphoblastic leukemia cells. By the some experiments on these cells, the curcumin lowers the phosphorylation and inhibit the above constitute cells in chronic lymphoblastic leukemia (Xu & Li, 2012). By treating the curcumin the XIAP expression, which gradually decreased and some elevation in the apoptosis of curcumin and down the target of NF-kB pathway. The STAT-3 activity is evacuated and lowering the expression of Mcl-1, by the treatment of curcumin in most of the chronic lymphoblastic leukemia, generally curcumin inhibit the AKT, BIM which regulates the AKT, the pro-apoptotic protein (Shanbhag, 2017).

5 Conclusion and future perspectives: Generally leukemia is incurable by present treatments. Several transplantation and some other anti-tumour drugs for leukemia having a notable side effects. And the treatment, available now also not cost effective and it is hectic for economically weaker patients. But the alternative source and natural spice curcumin shows many therapeutic effect against many tumours and also clinically proven. Naturally curcumin has an anti-leukemia property and shows an wide range of activity on different leukemia cells and has no side effects. It also shows greater effect on early stages of chronic lymphoblastic leukemia. curcumin prevents the process and inhibit and induce proliferation and apoptosis in leukemia. It shows better effect when administered with conventional anti-tumour drugs and other therapeutic agents and has the benefit of less dose and side effects with conventional drugs. Using nanotechnology and chemically modifying and changing the hydrophobic Content, it shows greater bioavailability, because of the lesser bioavailability of the curcumin, to need of this should impose lots of research on it. As using curcumin as for an anti-leukemia therapy, to be taken for longer term for an better effect. There is no any clinical data against the safety and long term use of curcumin. To assess the better safety and efficacy of the curcumin in different types of leukemia and other tumours need to propose long term clinical trials against the curcumin in humans. Some other researches also proposed that curcumin free turmeric also shows an anti-tumour and anti-inflammatory activity. The oil content present in the curcumin shows better bioavailability. It also suggest that for long term use of curcumin in leukemia, here we need of more research on curcumin.
6. REFERENCES:


