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Review Article

Leukaemia: Insights into Aetiology, Incidence, Classification, and Treatment

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Abstract: Background: Leukaemia is a complex form of blood cancer characterized by the rapid proliferation of abnormal white blood cells and the uncontrolled accumulation of these cells within the bone marrow and lymphoid tissue**.** The main cause of leukaemia remains unknown**. Objectives:** The aim of the present review is a high light on the aetiology, incidence, classification, and treatment of leukaemia with chemotherapy, and some polyphenols uses to enhance the effect of chemotherapy and reduce the required dose to induce cell death in cancer cells. The disease's occurrence has been linked to a combination of both variant environmental aspects and human genetics. Long-term exposure to certain industrial chemicals and exposure to high levels of radiation energy. Smoking has also been linked to doubling or tripling the risk of acute myeloid leukaemia. Generally, incidence of leukaemia occurs at varying rates according to age and gender, and according to which it appears to be more common in men than in women; moreover, the incidence rate is higher in adults than in children. Four types of leukaemia have been identified: acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia and chronic myelogenous leukaemia. The treatment options for leukaemia depend on the type of leukaemia, a patient's age and their general health. There are many types of treatments for treating leukaemia, such as chemotherapy, immunotherapy, radiotherapy and bone marrow transplant. Chemotherapies are known as the most common type of leukaemia treatments. Although chemotherapy has the ability to kill leukaemia cells, it causes cytotoxicity to normal cells that are not able to renew themselves following chemotherapy. Polyphenols are an essential part of the human diet, where flavonoid and phenolic acids show the majority of polyphenol existent in vegetables and fruits such as pomegranate. Polyphenols have been divided to three different classes: flavonoids (apigenin), stilbene (cis-stilbene) and anthraquinone (emodin and rhein). These different polyphenol classes have shown the ability to work in an anti-proliferation, pro-apoptotic manner to prevent the progression of solid tumours. **Conclusion:** It can be concluded that leukaemia is a complex form of blood cancer, which the main cause of it remains unknown. The occurrence of the disease has been linked to a combination of both variant environmental aspects and human genetics. The incidence of leukaemia occurs at varying rates according to age and gender. There are many types of treatments for treating leukaemia. Chemotherapies are known as the most common type of leukaemia treatments. Polyphenols have anti-cancer properties that are attributed to their ability to work as antioxidants. Therefore, the patients should be advised to take vegetables and fruits which rich in polyphenols while they are treated with chemotherapy to decrease its harmful effects.

Keywords: Leukaemia, Aetiology, Incidence, Classification, Treatment, Chemotherapy, polyphenols.

1. Introduction

Leukaemia is a complex form of blood cancer characterized by the rapid proliferation of abnormal white blood cells and the uncontrolled accumulation of these cells within the bone marrow and lymphoid tissue (Dahlawi *et al*. 2012). These cells are not able to function appropriately to fight against infection, which leads to the impaired ability of bone marrow to produce normal haematopoietic cells such as red blood cells and platelets (Hoffbrand and Moss 2011). Cells grow abnormally as a result of a genetic defect; normal blood cells die, and are replaced by immortalised cancerous leukaemic cells (Buffler *et al*. 2005; Dahlawi *et al*. 2012).

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2. The aetiology of Leukaemia

The main cause of leukaemia remains unknown. However, the disease's occurrence has been linked to a combination of both variant environmental aspects and human genetics (inherited) (Buffler *et al*. 2005; Hutte 2010). Other factors linked to an increase in leukaemia development are: long-term exposure to certain industrial chemicals such as benzene and exposure to high levels of radiation energy (Buffler *et al*. 2005). Smoking has also been linked to doubling or tripling the risk of acute myeloid leukaemia (AML) (Spitz *et al*. 1990; Buffler et al. 2005). Gender and age can also have an impact, where chronic myeloid leukaemia (CML) and AML have been found to be more common in men than in women, and acute lymphoid leukaemia is expected to increase with age (Hjalgrim *et al.* 2003)**.** Genetics also play a key role in the aetiology of leukaemia. For instance, although most leukaemias have no link with family history, first degree relatives with chronic lymphoid leukaemia (CLL), or who have an identical twin who has or has had AML or acute lymphoid leukaemia (ALL) may increase their risk of developing leukaemia (Rauscher *et al*. 2002). Finally, genetic abnormalities are also known as key risk factors related to certain types of leukaemia. For example, there are a number of syndromes that occur as a consequence of genetic mutations present at birth, which may cause an increase in the risk of developing leukaemia. These include black fan-diamond syndrome, Bloom syndrome and Fanconi anaemia. In addition, Down syndrome, which is a chromosomal 21 abnormality, is associated with an increased risk of developing leukaemia (Weng *et al*. 2004).

3. Incidence of Leukaemia

Leukaemia makes up approximately 3% of all incidence of cancer worldwide, with about 257 000 cases of leukaemia being diagnosed each year. The incidence rate varies from 1 to 12 individuals per 100 000 among the UK population for all types of leukaemia (Cancer Research UK 2013). Generally, a high incidence is obvious in the USA, Western Europe, Canada and Australia, whereas in Africa and Asia, the incidence rate has generally been low. Leukaemia has been found to be the 11th most common cancer in the UK, where about 8600 individuals are affected with this disease and approximately 4300 patients die each year (Cancer Research UK 2013). In the USA, more than 40 000 cases were estimated to have been diagnosed with leukaemia in 2012. In addition, about 82 300 new cases of leukaemia were diagnosed in Europe in 2012 (Rosenberg *et al.* 2012).

Generally, incidence of leukaemia occurs at varying rates according to age and gender, and according to which it appears to be more common in men than in women; moreover, the incidence rate is higher in adults than in children (Hjalgrim *et al*. 2003). Leukaemia causes nearly 33% of all cancer deaths in children, where acute lymphoblastic leukaemia constitutes almost 55% of all types of blood cancer diagnosed among children younger than the age of five (Cancer Research UK 2013). In the USA, new cases of leukaemia are estimated at 74% of the total cases among children. According to leukaemia and lymphoma research, approximately 2200 individuals are affected by AML in the UK each year. However, in the USA, more than 14 500 cases in adults were diagnosed with AML and about 10 370 deaths from this blood malignance were recorded (American Cancer Society 2013). Although leukaemia is known as the most common cancer among infants, more than 9 in 10 cases have been detected in adults; in people aged 75 or older, about 4 in 10 cases are diagnosed (Cancer Research UK 2013).

The mortality rate of leukaemia patients is very low in people under the age of 50; however, it has shown a dramatic increase in people aged over 60 (Cancer Research UK 2013). In contrast, the mortality rate of AML in the USA indicated a significant increase in 2005 compared to the previous five years, whereas CML showed a decrease during the same period (Cancer Research UK 2013; Radich 2010). In 2015, it is estimated that the number of new cases of AML in the USA will be about 20 830 and 10 460 deaths (American Cancer Society 2015).

4. Classification of Leukaemia

Although many classification methods are used for classifying the different types of leukaemia, the World Health Organisation's (WHO) classification is known as the most widely used and where types of leukaemia have been classified depending on the origin of the cell to lymphoid and myeloid and based on the rate of progression to an acute status, which means that the disease rapidly progresses and immature cells are accumulated in bone marrow and blood, or alternatively, chronic status, where the disease progressed slowly and allows for the formation of small amounts of mature cells (Vardiman 2010). According to this classification, four types of leukaemia have been identified: acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia and chronic myelogenous leukaemia.

4.1. Acute Lymphocytic leukaemia (ALL)

Acute lymphocytic leukaemia, also known as acute lymphoid or lymphoblastic leukaemia, is identified by an increase in the number of blast cells. This type of leukaemia can be sub-classified according to precursor, which is either T or B lineages, and is considered the most common type among children (Vardiman 2010).

4.2. Chronic Lymphocytic Leukaemia (CLL)

This is a low-grad non-Hodgkin type of lymphoma that is more common among older people. In some cases, small numbers of CLL cells are found in the blood. However, they are detected in large numbers in

lymph nodes. This type is therefore called small lymphocytic lymphoma (SLL) (Ye and Song 2005).

4.3. Acute Myelogenous Leukaemia (AML)

This type of blood malignancy affects adults and it is more common in men than in women. It is also referred to as acute myeloid leukaemia, acute granulocytic leukaemia, acute myeloblastic leukaemia and acute nonlymphocytic leukaemia, all of which are sub-classes of this particular type (Colvin and Elfenbein 2003).

4.4. Chronic myelogenous leukaemia (CML)

Chronic myelogenous leukaemia**,** also called chronic granulocytic leukaemia, is a disease characterized by the BCR-ABL constitutive tyrosine-kinase (TK) oncoprotein. This disease results from a balanced mutual translocation between chromosomes 9 and 22 (t (9; 22) (q34; q11) (Lin and Li 2013). The encoding protein is considered the main pathogenic of the Philadelphia chromosome (Ph), which is recognised in nearly 95% of CML (Lin and Li 2013). Chronic myelogenous leukaemia typically occurs during middle age or after, and is rare in young children. In the UK, about 600 people are diagnosed with CML annually *(Calderón et al*. 2013).

5. Leukaemia Treatment

The treatment options for leukaemia depend on the type of leukaemia, a patient's age and their general health. There are many types of treatments for treating leukaemia, such as chemotherapy, immunotherapy, radiotherapy and bone marrow transplant (Appelbaum *et al*. 2006). In addition, newer therapies have recently been used, for example, Imatinib, which is a type of tyrosine kinas inhibitor that works specifically as a target for the activated tyrosine kinase domain of the Bcr-AbL fusion gene, present in the majority of CML. Imatinib primarily interacts with DNA, but can also generate reactive oxygen species (ROS), which damage cell components (Gerber 2008). Doxorubicin (DOX) is a powerful anthracycline antibiotic used against many human neoplasms, including acute leukaemias, lymphomas and sarcomas (Jakubowska *et al.* 2007). It has anti-proliferative properties and as a cytostatic drug can reduce RNA synthesis and may produce reactive oxygen species (ROS), resulting in cells' death by DNA damaging; it can also intercalate with DNA (Hamlaoui *et al*. 2012). However, Doxorubicin may have some side effect such as the development of cardiomyopathy and heart failure, and may cause cardio-toxicity if used for a long period of time, thus limiting its clinical uses (Hamlaoui *et al*. 2012).

Chemotherapies are known as the most common type of leukaemia treatments; however, they are expensive, mutagenic, carcinogenic or teratogenic, and have considerable side effects that cause poor prognosis, resulting in patients withdrawing themselves from these types of treatments. Although chemotherapy has the ability to kill leukaemia cells, it causes cytotoxicity to normal cells that are not able to renew themselves following chemotherapy, for example, hair cells and damage to normal blood cells and tissue (Banfi *et al*. 2001). Furthermore, cells may undergo metastasis or develop drug resistance (Deng and Zhang 2010).

For all of the above reasons, it is important to discover new treatments that can enhance the survival rate among leukaemia patients. A particularly interesting area where this is concerned is the use of bioactive agents from natural sources (Dahlawi*et al*. 2012). For example, polyphenols and polyacetylenes, which are two groups of bioactive components that have demonstrated potential roles in cancer treatments (Dahlawi*et al*. 2013). A number of researchers have shown that a diet rich in polyphenols – e.g., fruits and vegetables – have shown considerable improvements in quality of life and for progressing the survival rates of patients with cancerous diseases (Han *et al*. 2007; Dai and Mumper 2010). Polyphenols are an essential part of the human diet, where flavonoid and phenolic acids show the majority of polyphenol existent in vegetables and fruits such as pomegranate. These have anti-carcinogenic impacts in *vivo* and in *vitro* by modulating vital mechanisms in cells that are related to carcinogenesis; for example, disturbing the cell cycle and the induction of apoptosis (Ahn *et al*. 2003; Hafeez *et al*. 2008). Therefore, inhibition of the proliferation of tumour cells and apoptosis induction in these cells has become potential targets for cancer treatments (Dorai and Aggarwal 2004).

Polyphenols have anti-cancer properties that are attributed to their ability to work as antioxidants. As is known, free radical scavenging and metal chelating are antioxidant actions and the ability of polyphenols to chain breaking has been attributed to their ability for attacking free radicals (Piotrowska *et al.* 2012). Numerous studies have noted the increased depletion of glutathione (GSH) in malignant cells than in normal cells when they are treated with polyphenols such as those extracted from green tea (Gupta *et al*. 2000; Paschka *et al*. 1998). Normal cells are less susceptible to cytotoxic destruction by polyphenols as a result of their ability to preserve an intracellular redox status with adequate supply of GSH (Yamamoto *et al*. 2004; Chan *et al*. 2006).

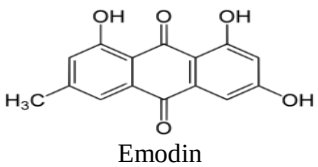
According to Mahbub *et al*. (2013), polyphenols have been divided to three different classes: flavonoids (apigenin), stilbene (cis-stilbene) and anthraquinone (emodin and rhein). These different polyphenol classes have shown the ability to work in an anti-proliferation, pro-apoptotic manner to prevent the progression of solid tumours (Huang *et al*. 2007; Dai and Mumper 2010). Numerous reports have shown that polyphenols exhibit anti-cancerous activity and are apoptotic in a number pro- of solid tumours, as well as a

number of leukaemic cell lines. Recently, they have demonstrated great effect on leukaemia cell lines compared to non-tumour blood cells (CD34+); this effect varied according to the type of leukaemia cell lineage (myeloid or lymphoid) (Mahbub *et al*. 2013).

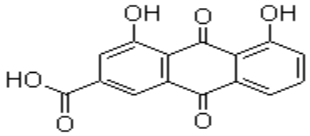
Emodin (1, 3, 8-trihydroxy-6-methylanthraquinone) and rhein (1, 8-dihydroxy-3-carboxyanthraquinone) are two types of anthraquinone derivative isolated from the roots, moulds and lichens of many plants such as rhubarb root (*Rheum palmatum*) (Huang *et al.* 2007). These organic compounds (Figure 2) have indicated a potential effect on leukaemia cells (Mori *et al*. 2012). Chen *et al*. (2002) showed that, emodin can induce apoptosis in HL-60 by activating the caspase-3 cascade, which appears to be ROS independent. In contrast, other studies have shown that apoptosis generated by emodin was mediated by ROS (Jing *etal.* 2002), caspase and mitochondrial dependent pathways (Srinivas *et al*. 2003). Furthermore, emodin has an apoptotic effect in human lung squamous cell carcinoma and HepG2 cells, which was mediated by activating p53, p21, Fas/APO1 and caspase-3 (Zhang *et al*. 1999; Shieh *et al*.2004). This type of polyphenol stimulates Bcl-2 and Bax modulation, releasing mitochondrial cytochrome c and activation caspase, leading to apoptosis (Su *et al*. 2005). It induces apoptosis through the caspase-3 dependent pathway in human proximal tubular epithelial HK-2 cells (Wang *et al*. 2007). Therefore, a number of researchers have shown that emodin appears to be apoptosis inducer and cell proliferation inhibitor, and that it is able to prevent metastasis by activating tyrosine kinases, protein kinase C (PKC), phosphoinositol kinase (PI3K), NF-kappa B (NF-κB) and (MAPK) signalling cascades (Huang *et al*. 2005).

According to Mahbub *et al*. (2013), emodin can induce the accumulation of cells at the G0/G1 phase in almost all leukaemia cell lines and is able to stimulate about 50% of apoptosis in Jurkat, THP-1, MOLT3, U937 and HL-60 leukaemia cell lines.

Rhein has also been shown to trigger cell death by blocking the uptake of glucose in tumour cells, which produced alterations in membrane related functions and triggers cell death (Castiglione *et al*. 1993). However, rhein presented a low effect on leukaemia cell lines; (Mahbub *et al.* 2013). A similar effect was also previously demonstrated in solid tumours (Li *et al*. 2011).



Emodin



Rhein

Figure 1. The chemical structure of anthraquinone: (Emodin and Rhein) (Mahbub *et al*. 2013).

Apigenin (4, 5, 7-trihydroxyflavone) is a type of flavone that is a dietary compound for many naturally occurring glycosides, as shown in Figure 3. It has been reported by (Wei *et al*. 1990; Birt *et al*. 1997) that apigenin has an anti-tumour impact against different malignant cell lines, e.g., skin carcinogenesis. In addition, it has the ability to inhibit cell growth, arrest cell cycles and induce apoptosis in breast, colon, liver and leukaemia cell lines (Way *et al*. 2004).

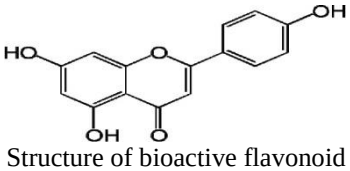


Figure 2. Structure of bioactive flavonoid Apigenin (Mahbub *et al*. 2013)**.**

Significantly, it has been found that apigenin induces the production of glutathione transferase (GST), an enzyme that is able to protect cells against free radical damage by increasing the resistance to oxidative stress caused by hydrogen peroxide (Fiander and Schneider 2000). GST also plays a protective role against malignancy, which aids the detoxification of mutagenic xenobiotics (Dirven *et al*. 1995).

It has previously been indicated that the overexpression of cyclooxygenase-2 (COX-2) plays a significant role in carcinogenesis (Chan *et al*. 1999). Therefore, studies have shown that apigenin inhibits COX-2 expression by modulating the upstream stimulatory factor (USF) in the upstream region of the COX-2 gene, or by mediating T-cell-restricted intracellular antigen 1-related protein (TIAR) to prevent the expression of COX-2 (Van Dross *et al*. 2007). Apigenin has also been shown to inhibit cell cycle progression and cause arrest at G_2/M, which is believed to be associated with the suppression of P34 (Van Dross *et al*. 2007). Apigenin has also been shown to cause G1 cell cycle arrest through the suppression of cyclin-dependent kinase (Cdk2) activity and the inhibition of p21/WAF1. In addition, apigenin also induces alteration in the localization of Bax and in releasing cytochrome C from mitochondria (Lepley and Pelling 1997).

Apigenin treatment stimulated changes in Bax/Bcl 2 in order to induce apoptosis in the human prostate (Shukla and Gupta 2004). However, it induced the activity of caspase-3 and cleavage of poly-polymerase, causing a reduced mitochondrial

transmembrane, released mitochondrial cytochrome c into the cytoplasm and then induced the processing of procaspase-9 (Wang *et al*. 1999). Mahbub *et al*. (2013) showed that apigenin has been shown to stimulate apoptosis in all leukaemia cells, and was able to induce an increase in caspase-3, representing early apoptosis and a change in morphology, this explaining the late stages of apoptosis in some cell lines such as K562 and KG-1a.

Cis-stilbene (cis-2, 3-Diphenyloxirane) is classified as a stilbene that is a highly conjugated compound. The phenyl ring in this type of stilbene exhibits sterical interaction (Figure 4). It has been reported that cis-stilbene can induce apoptosis in cancer cells. It is believed to act independent on p53 and stimulates rapid perinuclear mitochondrial clustering (Polyak *et al*. 1997). However, as previously shown, mitochondria play an important part in the p53-dependent apoptotic pathway and p53 may have direct involvement in mitochondria-mediated apoptosis (Moll *et al*. 2005). Some types of cis-stilbene components can initiate apoptosis cascade in cancer cells and perinuclear mitochondrial clustering was one of the first events presented. Although p53 and p21 have critical roles in mitochondria-mediated apoptosis, these were not needed in the apoptotic action of cis-stilbene. Therefore, mitochondrial clustering, or the upstream actions that cause mitochondrial clustering, may be a common reason for apoptosis stimulated by cis-stilbene polyphenols (Lee *et al*. 2004).

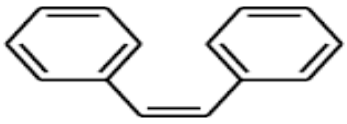


Figure 4. Chemical structure of cis-stilbene (Mahbub *et al*. 2013).

Cis-stilbene has been shown to stimulate cell accumulation in the G_2/M phase in lung cancer cell lines (Lee *et al*. 2004). In addition, it has been shown to induce accumulation in the S-phase in HL-60 and at the G0/G1 phase in many types of leukaemia cell lines, including the HL-60 cell line (Mahbub*et al*. 2013).

6. Conclusion

It can be concluded that leukaemia is a complex form of blood cancer, which the main cause of it remains unknown. The occurrence of the disease has been linked to a combination of both variant environmental aspects and human genetics. The incidence of leukaemia occurs at varying rates according to age and gender. There are many types of treatments for treating leukaemia. Chemotherapies are known as the most common type of leukaemia treatments. Polyphenols have anti-cancer properties that are attributed to their ability to work as antioxidants. Therefore, the patients should be advised to take vegetables and fruits which rich in polyphenols while they are treated with chemotherapy to decrease its harmful effects.

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