Review

Siddhi Manohar Bagwe[1] / Pravin Popatrao Kale[1] / Lokesh Kumar Bhatt[1] / Kedar S. Prabhavalkar[1]

Herbal approach in the treatment of pancytopenia

[1] Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai campus, Vile Parle (W), Mumbai, India, E-mail: pravinpkale@gmail.com

Abstract:
Pancytopenia is a health condition in which there is a reduction in the amount of leucocytes, erythrocytes and thrombocytes. If more than one of the blood cells is low then the condition is called as bicytopenia. The pancytopenic condition is observed in treatment of diseased conditions like thalassemia and hepatitis C. Iatrogenically pancytopenia is caused by some antibiotics and anti-HCV drugs. Medical conditions like aplastic anaemia, lymphoma, copper deficiency, and so forth can also cause pancytopenia. Pancytopenia can in turn decrease the immunity of the person and thereby can be fatal. Current therapies for pancytopenia include bone marrow stimulant drugs, blood transfusion and bone marrow transplant. The current therapies are very excruciating and have long-term side-effects. Therefore, treating these condition using herbal drugs is very important. Herbs like wheatgrass, papaya leaves and garlic are effective in treating single lineage cytopenias. The present review is focused on the potential effects of natural herbs for the treatment of pancytopenia.

Keywords: bone marrow transplant, herbal approach, leucopenia, pancytopenia, papaya leaves

DOI: 10.1515/jcim-2016-0053

Received: June 5, 2016; **Accepted:** October 18, 2016

Introduction

The blood cells are formed in the bone marrow by the process of haematopoiesis, where the multipotent haematopoietic stem cells also called as haemocytoblasts, mature to give a common myeloid progenitor to in turn give erythrocytes, leucocytes and thrombocytes. In pancytopenia, either bone marrow, haemocytoblasts or directly the cells get damaged, so as to cause the condition. Pancytopenia is broadly classified into single lineage pancytopenia and multi-lineage pancytopenia. In single lineage pancytopenia, only one cell type is reduced in the number, whereas in multi-lineage pancytopenia more than one cell type is reduced (Figure 1) [1]. Pancytopenia is majorly caused in the patients suffering from megaloblastic anaemia and aplastic anaemia. The other causes are some viral infections like HIV, HCV. Chemicals like benzene, autoimmune disorders like rheumatoid arthritis, and medicines like methotrexate, chloramphenicol also can cause pancytopenia. The occurrence of pancytopenia lies between the ages of 2 years to 86 years. In India, annually there are 20 % deaths due to improper treatments and due to late diagnosis. The prevalence still remains unknown, due to various causes of pancytopenia. Gestational pancytopenia still remains the major cause of death. Drug-induced and disease-induced pancytopenia also are the leading causes of death. Diagnosis can be done by bone marrow examination, which is done by bone marrow aspiration. Bone marrow aspiration is very excruciating and is generally done by a specialized physician. Also a detailed clinical history is checked to diagnose the disease. The symptoms include tiredness, fatigue, puffiness of face, oedema, lassitude, and reduced ability to perform, i. e. effort intolerance. The clinical observations include reduced number of leucocytes, erythrocytes and thrombocytes in the blood [1]. Due to such painful therapies, an alternative to these therapies should be discovered. Herbal approach is one of the areas from where newer drugs can be found for the treatment of pancytopenia. Currently, bone marrow stimulant drugs like Epoetin alfa (Epogen, Procrit), Filgrastim (Neupogen), Pegfilgrastim (Neulasta), Sargramostim (Leukine, Prokine) are given for the treatment of cytopenia. These are basically DNA recombinant human cell stimulating factors. There are many side-effects related to these therapeutic regimens. Therefore ascertaining some alternate drugs is the need of the day [1].

Pravin Popatrao Kale is the corresponding author.

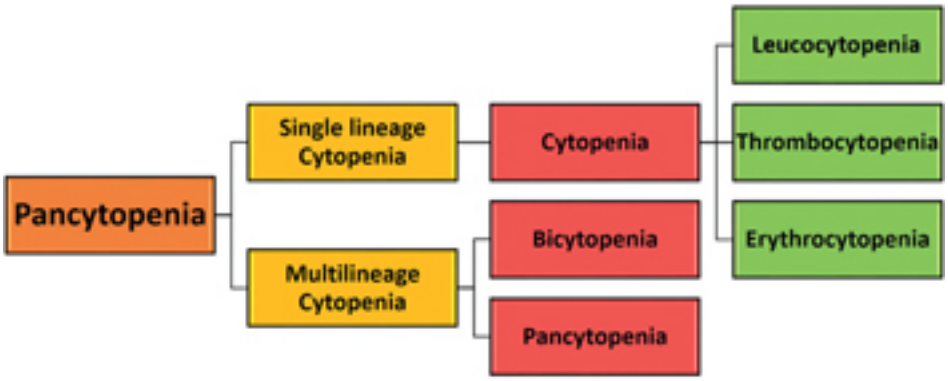

Figure 1: Types of pancytopenia [1].

Causes of pancytopenia (Figure 2)

Figure 2: Causes of pancytopenia [2–13].

Causes of pancytopenia can be generally classified into:

1. Idiopathic [2]
2. Iatrogenic [3–5]
3. Disease induced [6–10]
4. Chemical toxicity [11]
5. Drug induced [8, 12, 13]

Idiopathic

Some causes of pancytopenia remain unknown, especially in children [1]. This type of pancytopenia is called idiopathic pancytopenia. Idiopathic Aplastic Anaemia was the common cause of idiopathic type of pancytopenia [2]. Idiopathic type of pancytopenia can be fatal, as the cause of cytopenia is unknown and therefore the patient is unaware of the condition.

Iatrogenic

In Iatrogenic type of pancytopenia, the condition occurs because of some another medical treatment or examination. Generally, chemotherapies and radiotherapies cause pancytopenia [3]. Bone marrow suppression and bone marrow transplant can also lead to pancytopenia. Some drug therapies like immunosuppressant therapy of azathioprine in inflammatory bowel diseases can cause pancytopenia [4, 5].

Disease induced

Disease-induced pancytopenia is commonly seen, as the prevalence of disease-induced pancytopenia is more as compared to other causes of pancytopenia. Graves' disease [6], Crohn's disease [7], leukaemia [8], hypersplenism [9], aplastic anaemia [10]. Pancytopenia remains the secondary cause in these types of diseases. The pancytopenia occurs due to immune suppression, autoimmune activity, bone marrow infection or reduction in the haematoblasts.

Chemical toxicity

Chemicals like benzene are haematotoxic and cause toxicity of bone marrow, therefore leading to pancytopenia [11]. It causes acute pancytopenia on consumption and therefore is fatal, if not treated on time. Benzene damages the bone marrow and therefore stops the haematopoiesis and in turn the production of cells, which causes pancytopenia.

Drug induced

Most of the anti-cancer and anti-viral drugs cause pancytopenia, as they directly target the cells. As the infected cells are targeted, the normal cells are also damaged in some proportion, which causes pancytopenia. Methotrexate which is used to treat leukaemia, commonly causes pancytopenia [8, 12]. The interferon and ribavirin therapy which is a therapeutic regimen for the treatment of hepatitis C also causes a severe pancytopenia [13].

Recent cases reported for pancytopenia

- Levetiracetam (Keppra) is an anti-epileptic drug which modulates the neurotransmitter release has shown pancytopenia as one of its side-effects [14]. The prevalence of pancytopenia was 3.82 % with levetiracetam treatment (Figure 3) [15]
- There is a recent case reported for patients with hereditary folate malabsorption to have reversible pancytopenia. Folate malabsorption can be the cause for pancytopenia (Figure 3) [16].Patients with Crohn's disease had recurrent pancytopenia in 5–3.8 % due to the absorption of 6-mercaptopurine (Figure 3) [4, 7, 17].
- Pancytopenia induced by low dose of methotrexate is widely seen. Out of the patients taking methotrexate, around 3 % of the patients suffer from pancytopenia. This is an example of drug-induced pancytopenia (Figure 3) [12, 18].
- Acute myeloid leukaemia or acute lymphoblastic leukaemia observed with pancytopenia among 11.9 % patients (Figure 3) [19, 20].

– Peg-interferon and ribavirin therapy in the patients suffering from Hepatitis-C causes drastic reduction in the number of blood cells, therefore exacerbating the pancytopenic condition [13]. Peg-interferon and ribavirin therapy related prevalence was 3.4 % (Figure 3) [21].

– Patients with pituitary oedema also tend to suffer from pancytopenia and Panhypopituitarism. It is said that the hormones also play a very important role in the management of pancytopenia [22]. The reported prevalence of pancytopenia in patients with pituitary oedema was 15 % (Figure 3) [23].

– The use of trabectedin in the treatment of prostate and breast cancer was associated with severe cytopenia in 51.35 % patients and death (Figure 3) [24, 25].

– Pancytopenic condition was seen in the patients suffering from methylmalonic acidemia [26].

– Sheehan syndrome or Simmond syndrome is a condition of hypopituitarism caused by necrosis due to blood loss which results in decreased number of blood cells and resultant pancytopenia [27]. The reported prevalence of pancytopenia in patients with Sheehan syndrome or Simmond syndrome was 15 % (Figure 3) [23, 28].

– Systemic lupus erythematous is an auto-immune disease. Its association with pancytopenia can be due to failure to recognise between self and non-self cells by immune system [29]. The reported prevalence of pancytopenia was 20–70 % depending on the severity (Figure 3) [30].

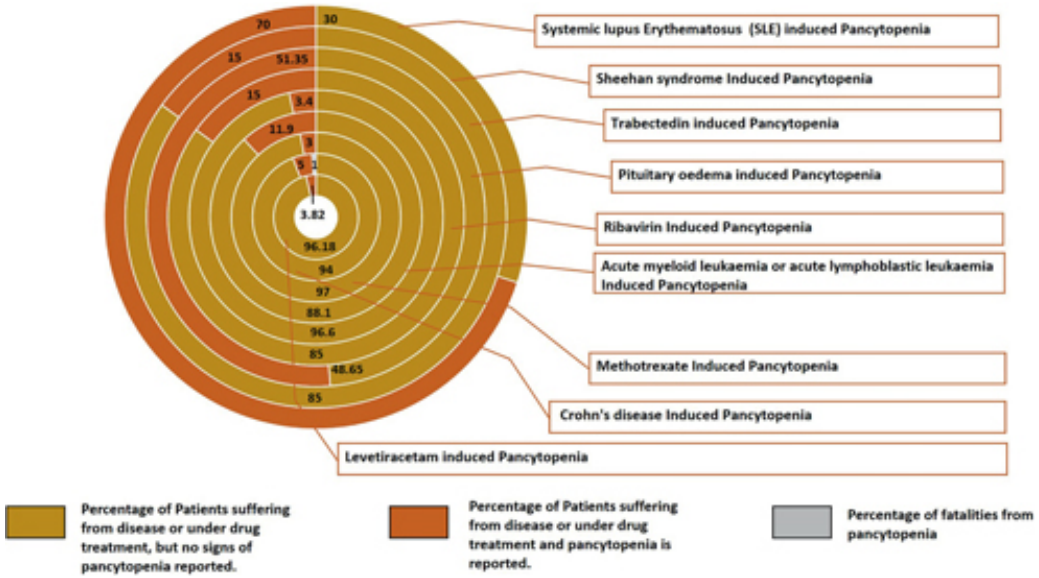

Figure 3: Prevalence of pancytopenia for recent cases [4, 12, 15, 17, 20, 21, 23, 25, 28, 30].

Current therapies

The current therapies are listed as follows:

1. Bone marrow stimulant drugs [31–35]
2. Blood transfusion [36]
3. Bone marrow transplantation [37–39]
4. Stem cell therapy [40]

Bone marrow stimulant drugs

Bone marrow stimulant drugs are often used in the pancytopenia, as the major therapy. In this therapy, they inject the bone marrow stimulant drugs, which are generally colony-stimulating factors. These colony-stimulating

factors, over-express the levels of cytokines, which in turn increase the colony-forming units and therefore, increasing the cell production [31]. Sargramostim is one of the colony-stimulating factors, which stimulates the hematopoietic progenitor differentiation to monocytes and neutrophils, which increases the neutrophils and therefore, reduces the threat of neutropenia [32]. Sargramostim is produced with the help of yeast, therefore can cause hypersensitivity in patients on chronic use. Filgrastim is another widely used granulocyte colony-stimulating factor which is used for stimulating the differentiation and proliferation of granulocytes. It is a recombinant DNA technology product. The side-effects include mild to severe bone pain, hypersensitivity reactions, ruptured spleen, haemoptysis and alveolar haemorrhage [33]. Epoetin alfa is a synthetically produced human erythropoietin, which is manufactured using DNA recombinant technology [34]. It stimulates the process of erythropoiesis and is used to increase the productions of erythrocytes in the body. The side-effects of epoetin alfa include joint pain, allergic reactions, pulmonary embolism, etc. It can also increase the levels of haemoglobin and haematocrit abnormally to result in dyspnoea and it can be fatal [35]. As it is seen, the side-effects of colony-stimulating factors majorly include joint pain and hypersensitivity. On, chronic use, the side-effects can be more prevalent and the harm caused to the patient will be more. Also, inadequate dosing can be fatal, as it can invariably increase the levels of colonies and in turn lead to anaphylactic shock.

Blood transfusion

Blood transfusion is commonly done for diseases like thalassemia, where the body fails to produce normal erythrocytes due to defect in the haemoglobin. It is genetic and therefore passed through the families. Blood transfusion is done once in 21 days, as the number of blood cells is utilized down the line. Therefore, the pancytopenic condition is observed in the later days after blood transfusion. Patients with thalassemia often are prone to viral diseases like hepatitis C, for which the ribavirin and interferon therapy is given. During this therapy also pancytopenic conditions are observed. Therefore, colony-stimulating factors are given and also the span for which blood is transfused is reduced. This procedure is very painful and as the transfusion is to be done once in 21 days, it is tedious. Also, it can cause opportunistic infections like hepatitis C [36].

Bone marrow transplantation

In bone marrow transplantation, the destroyed or the damaged bone marrow is replaced with the healthy one. The bone marrow transplantation can be autologous, where the stem cells are removed and a radiotherapy or chemotherapy is given to destroy the whole bone marrow, and then the stem cells are injected back to produce normal cells [37]. In the pancytopenic conditions, as the bone marrow transplantation is done, the damaged bone marrow is replaced with a healthy one, therefore normal blood cells are produced. It is very difficult and rare that the patient's stem cells are healthy and therefore the chances of autologous blood transplant are very rare, unless the umbilical cord stem cells are preserved. The other type of transplant is allogeneic stem cell transplantation, where the stem cell of the sibling or the donor with human leucocytes antigen matching is required. Bone marrow transplantation is a very costly procedure and the end stage therapy, where the person can get totally cured if the operation is successful. Some of the patients also suffer from graft vs host disease, where the stem cells from the donor are rejected by the recipient's body and therefore there is the graft rejection which causes hypersensitivity reactions [38, 39].

Stem cell therapy

Stem cell therapy is the use of the stem cells for the treatment of the diseases. Bone marrow transplantation is also a stem cell therapy, which is discussed in detail above. Induced pluripotent stem cells are recently studied to have potential to regenerate human tissues [40]. They also remain in controversy due to potential of human cloning. In the treatment of pancytopenia these stem cells are used so that the body can produce normal cells with the aid of pluripotent stem cells.

Herbal drugs and the treatment of pancytopenia

Currently, the therapies for the management of pancytopenia are very costly and have various side-effects as listed above. These therapies are very complicated and painful, therefore alternative treatment and newer drugs

is the need of the day. Herbal drugs are the drugs which have a plant origin. Some of the potent drugs which are used today for the treatment of major diseases are isolated from the plants or are either the structural modifications of the compounds which are isolated from the plants. Therefore, newer drugs for the treatment of pancytopenia are necessary. Few plants and herbs are under research for the treatment of pancytopenia. Plants listed in Table 1 are known to increase the blood cell production.

Leucocytopenia

- Garlic [41–46]
- Astragalus [47–53]
- *Uncaria tomentosa* [54–60]

Garlic: *Allium sativum* commonly known as garlic is generally known for its anti-microbial [41] and anti-hyperlipidaemic [42, 43] activity. It is under research for cancer and is meta-analysed for the same [44]. Garlic contains compounds like alliin, allicin, ajoene, diallyl polysulfides, vinyldithiins, S-allylcysteine, and enzymes, saponins and flavonoids [45]. Garlic was reported to be effective in increasing the leucocytes in the body after consumption. Therefore, it was studied and found that allicin [46] (Figure 4) was responsible for the elevation of leucocytes. Sulfhydryl compounds are responsible for cell growth and leucopoiesis. Compounds like L-cysteine can induce proliferation of leucocytes. Low –SH had been observed in leucocytopenic conditions. Therefore, the –SH group may be responsible for the activity. Flavonoids are potent anti-oxidants, responsible to decrease oxidative stress. Therefore, decreasing the cell death due to oxidative radical species [47]. The side-effects of allicin are generally regarded as mild and uncommon [48]. Rashes, wheezing and nausea can be seen with people allergic to garlic.

Astragalus: Astragalus is a genus containing 3,000 species. It is currently researched, for its effect in the treatment of cancer [49], hypertension [50], cerebral ischemia [51] and inflammation [52]. Astragalus is also researched for its potential benefits in the treatment in leucocytopenia [53]. Further, the recent studies aim that astragalus polysaccharides promotes the chemotactic ability and differentiation of the bone marrow granulocyte via the L-selectin signalling [54]. It is seen that the astragalus polysaccharides [55] (Figure 4) had increased polymorphonuclear leucocytes significantly than that of granulocyte colony-stimulating factor [54]. Astragalus polysaccharides have also proved to reduce the reactive oxygen species production, which in turn damage the cells and produce leucocytopenia [56]. Astragalus is generally considered safe in adults, but can cause various drug interactions. It may interact with drugs like cyclophosphamide and other immunosuppressant's. Few astragalus species can be neurotoxic, hence thorough identification and characterization needed before consumption [57].

Uncaria tomentosa: Generally known as cat's claw due to its characteristic claw-shaped thorns. They are currently researched for anti-inflammatory [58], anti-oxidant [58], denture stomatitis [59], haemorrhagic cystitis [60] and anti-fungal activity [61]. It has also claimed to have a leucocytopenic activity, especially the elevation of monocytes. The studies conclude that the compound mitraphylline [62] (Figure 4) which is a pentacyclic oxindolic alkaloid found in *Uncaria tomentosa* is responsible for the activation of the monocytes. Also, it regulates the plasticity of the monocytes and in turn of the macrophages [63]. *Uncaria tomentosa* water extracts without indole alkaloids showed significant increase in the levels of all the components of white blood cells [64]. Recently it was found that it also prolonged lymphocyte half-life and increased the number of spleen cells and therefore increases the number of splenic leucocytes. The compound from *Uncaria tomentosa* which was responsible for this activity was quinic acid (Figure 4) [65, 66]. Reported side-effects are headaches, dizziness, and vomiting pertaining to *Uncaria tomentosa*. Its consumption should be avoided during pregnancy as it may act as abortifacient [67].

Table 1: Herbal drugs which can be used for the treatment of pancytopenia [37, 44, 51, 54, 62].

Leucocytopenia	Thrombocytopenia	Erythrocytopenia
Garlic	Papaya leaves	Papaya leaves
Astragalus	wheatgrass	wheatgrass
Cat's claw	Pumpkin	Indian gooseberries
Chlorophyll	Spinach	Fenugreek
Wheatgrass	Indian gooseberries	Spinach

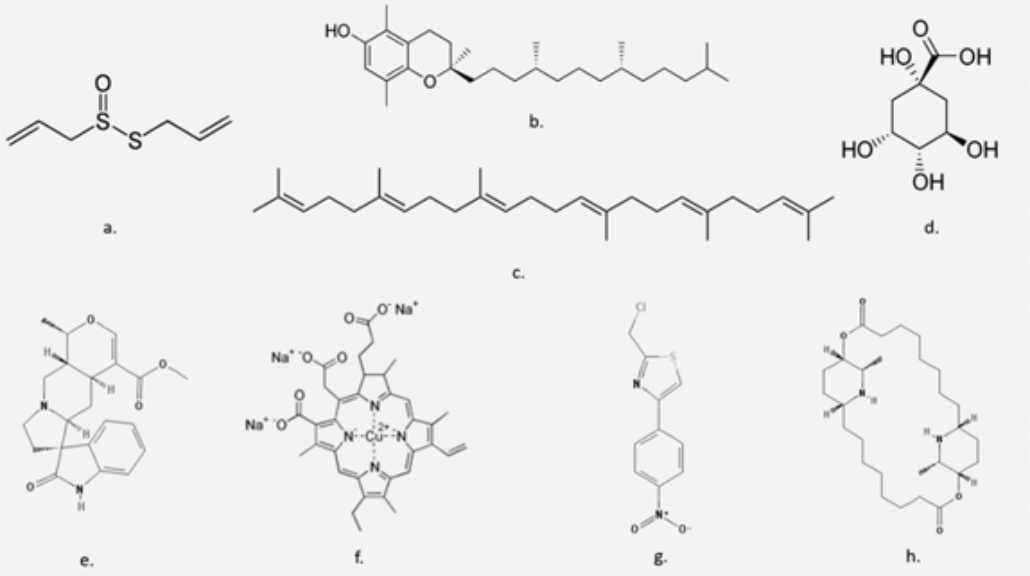

Figure 4: Structure of drugs which may alleviate pancytopenia; a. Allicin (*Allium sativum*), b. Tocopherol (*Cucurbita pepo*), c. Squalene (*Cucurbita pepo*), d. Quinic acid (*Uncaria tomentosa*), e. Mitraphylline (*Uncaria tomentosa*), f. Chlorophyllin – Sodium Copper salt (*Triticum aestivum*), g. Astragalus Polysaccharide (Astragalus), h. Carpaine (*Carica papaya*).

Thrombocytopenia

Pumpkin: The biological source of pumpkin is *Cucurbita pepo*. The main components of pumpkin plant are lutein, alpha and beta carotene which generates vitamin A in the body [68]. Compounds like tocopherol [69] and squalene [70] (Figure 4) found in the oil of the seeds of *Cucurbita pepo* are found to contribute to the oxidative stability [71]. The methanolic extract of the *Cucurbita pepo* seeds has found to have decrease the prothrombin time and increase the platelet count [72]. The pumpkin has shown to reduce the bleeding time, as the levels of platelets are increased [73].

Erythrocytopenia

Fenugreek: *Trigonella foenum-graecum* belonging to the family Fabaceae is a semi-arid plant found in the Indian subcontinents. The seeds of *Trigonella foenum-graecum* have proved to have anti-hyperglycaemic [74], anti-neoplastic [75], gastro-protective [76], anti-inflammatory [77], anti-pyretic [77], anti-radical [78] and anti-oxidant effect [78]. *Trigonella foenum-graecum* has also been found to have a role in stimulating the increase of erythrocytes by reducing the oxidative stress on them [79]. It has also been observed that the polyphenol rich extract of *Trigonella foenum-graecum* has proven to reduce the oxidative stress on erythrocytes [80]. The possibility of *Trigonella foenum-graecum* interacting with the cardiovascular drugs is high, therefore concomitant administration of cardiovascular drugs and herbal formulations containing *Trigonella foenum-graecum* should be avoided [81].

Herbal remedies for the treatment of bi-lineage cytopenia

Bi-lineage cytopenia is a type of pancytopenia where the body has either two of the blood cell reduction. The causes still remain the same as that of pancytopenia in general. Oxidative stress and cytotoxic drugs are generally responsible for bi-lineage cytopenias. The treatment is also similar to that of pancytopenia, but a combination therapy of granulocyte stimulating factors and other immunostimulant drugs is given to increase the levels of the blood cells. Related side-effects are also similar to pancytopenia and therefore consideration of alternate herbal approaches is important in its research.

Papaya leaves

Papaya, scientifically known as *Carica papaya*, commonly found in Asia, America and Mexico. In industries, the latex papain found in papaya is used for tenderizing of meat. It is been studied for it anti-tumour [82], immunomodulatory [82], anti-inflammatory [83] and hypo-glycaemic effect [84]. In Asia, the leaves of *Carica papaya* are widely used as a treatment for dengue fever [85]. No proper evidence is still found about its mechanism of action. It is reported that papaya leaves also have increased platelets and erythrocytes in the patients with dengue infection, where the platelets count is reduced. It is said that carpaine [86] (Figure 4) or papain may be responsible for the activity. Carica papaya have reported to induce thrombopoietic cytokines by hematopoietic and mesochymal stem cells [87]. Many papers have reported the effect of the leaves of *Carica papaya* to increase the levels of platelets, but the mechanism of action is still unknown. It is also seen that the aqueous extract boosts the erythropoiesis in the murine models [88]. *Carica papaya* is also studied for its anti-sickling and membrane stabilizing properties of the erythrocytes [89]. It also has anti-oxidant properties, thereby may help in reducing oxidative stress level on the cells. As *Carica papaya* is responsible to elevate the thrombocytes and erythrocytes, it can be used to treat bi-lineage cytopenia.

Herbal remedy for the treatment of pancytopenia

Wheatgrass

Scientifically known as *Triticum aestivum* are the cotyledons of the wheat plant [90]. It contains large amount of iron, phosphorus, magnesium, manganese, copper and zinc [90]. It also has rich source of tocopherols and vitamin E potency. The chlorophyllin present in the wheatgrass has bacteriostatic properties [91]. It also stimulates the production of haemoglobin and erythrocytes in anaemia [92]. Chlorophyllin [93] (Figure 4) administration has shown to increase the abundance of Hematopoietic stem progenitor cell. Also, it is observed that there was activation of pro-survival transcription factors Nrf-2 and NF-κB, which in turn increased the survival of bone marrow cells. It thereby enhanced the levels of colony-stimulating factors [94–96]. As the survival of bone marrow is increased, it can directly enhance the production of erythrocytes, leucocytes and thrombocytes and benefit in the treatment of pancytopenia. Wheatgrass juice is reported safe [97].

Conclusions

As there is an unmet need in the treatment of pancytopenia, newer therapies with the fewer side-effects and better efficacy are needed. Herbal drugs mentioned above are responsible for treating single lineage pancytopenia. Drugs like chlorophyllin can be possibly used for the treatment of pancytopenia. Other drugs can be used in combination for the treatment. As sulfhydryl compounds are responsible for the cell growth, compounds like S-allylcysteine and allicin can be used for the elevation of leucocytes. Papain may be used for the treatment of thrombocytopenia as it elevates the level of cytokines and also has cell membrane stabilizing properties. Chlorophyllin may be a potential candidate for treating multi-lineage pancytopenia but also specifically the erythrocytopenia. Interestingly, the combination of these compounds particularly having different mechanism and site of action may aid in the alleviation of pancytopenia and therefore, stabilizing the blood levels in the patient. However, further research is required to discover the potential benefits of herbal combinations in the treatment of pancytopenia.

Acknowledgement

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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