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A review on herbal drugs used in thalassemia and related disorder

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Abstract
Thalassemia is a genetic disorder that involves abnormal haemoglobin formation. The two main categories of Thalassemia are alpha and beta Thalassemia that are then divided into further subcategories. While some mild forms of Thalassemia might even go unnoticed and only cause mild anaemia and iron deficiency problems in patients, other more severe forms of Thalassemia can even result in death. Individuals with Thalassemia can get treatment according to the level of severity of their condition. In addition, the patient may experience mental and social problems due to the congenital nature of the disease and its lifelong duration. The psychosocial problems and treatment burdens of Thalassemia patients are very high. There are many studies about the prevalence and physical consequences of Thalassemia. However, there are not enough articles and researches describing the psychosocial effects of Thalassemia on patients and what can be done about these effects. For this reason, this paper focuses on the process of Thalassemia and the psychosocial problems it creates to contribute to the literature and to be a roadmap for better handling these patients.

Keywords: Thalassemia, hemoglobinopathies, newborn screening, bone marrow transplant

Introduction
- A genetic blood illness called thalassemia is characterised by abnormally low level of the oxygen-carrying protein haemoglobin and red blood cells.
- A hereditary condition known as Thalassemia results in improper haemoglobin synthesis [1-3].
- The alpha and beta "chains" of haemoglobin are defective in Thalassemia patients, and as a result, the haemoglobin that is produced is also defective. Problems arise in a patient with Thalassemia because the body lacks the healthy haemoglobin that is needed for proper oxygenation.
- In addition to having lower blood levels of haemoglobin, a person with Thalassemia also doesn't have enough high-quality haemoglobin. The patient's body is still making an effort to manufacture more haemoglobin and red blood cells at the same time. 4 However, because of a genetic defect in the haemoglobin being created in that person's body, the newly produced haemoglobin causes additional issues because an excess of harmful haemoglobin is produced. People who have Thalassemia [2, 5].

Types of thalassemia
Thalassemia has three primary kinds and two types.
1. Beta Thalassemia, which includes the subtypes major and Inter media
2. Alpha Thalassemia, which comprises the subtypes haemoglobin H and hydrops fetalis

Thalassemia beta
- A class of illnesses with a high prevalence worldwide and a sizable negative impact on both health and the economy is the beta Thalassemia [6].
- Patients with -Thalassemia major have severe chronic hemolytic anaemia and need blood transfusions on a regular basis starting in early childhood [7, 8, 9].
- The monitoring of illness complications, transfusion therapy, iron overload, and chelator toxicity are the main topics of the first section of this review.
- The authors evaluate recent advancements in beta thalassemia therapy in the second.

Section.

Due to decreased b globin chain production and, in rare cases, increased a globin gene dosage, beta thalassemias have a relative excess of a chains [10].

- The beta Thalassemia phenotype is determined by the degree of the imbalance and ranges from minimal effects in beta Thalassemia trait to severe transfusion-dependent anemia.
- Beta-thalassemia is classified into three main subgroups based on their clinical expression: major, Inter media, and minor. β-thalassemia major presents itself within the first 2 years of life with severe anemia, poor growth, and skeletal abnormalities and requires regular, lifelong blood transfusions.

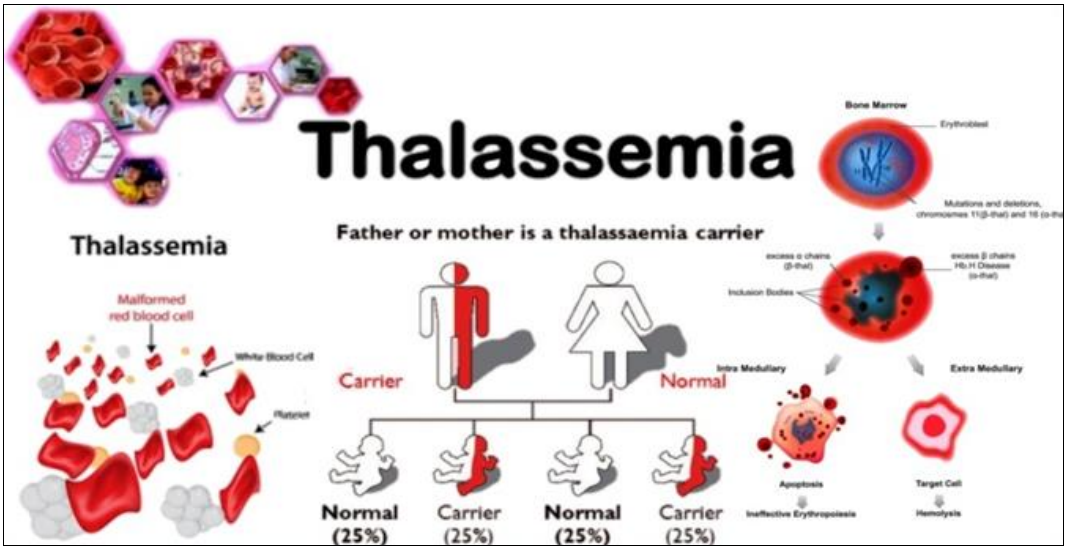

Fig 1: Thalassemia Information [4]

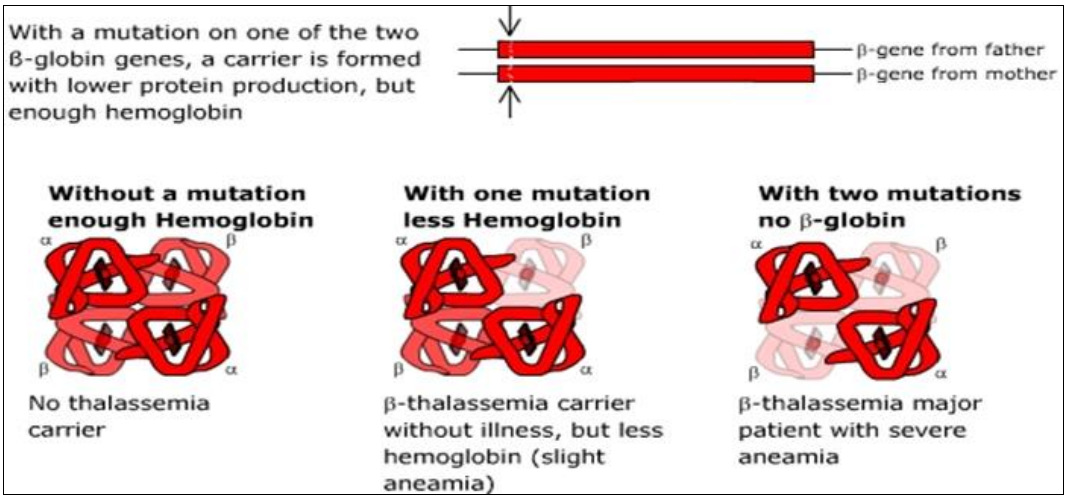

Fig 2: β Thalassemia [11]

Symptoms

- Anemia and inefficient erythropoiesis together cause beta thalassemia.
- JAK2 STAT5 signalling promotes erythroblast growth when erythropoietin levels are
- Elevated due to anemia; additional extrinsic and intrinsic RBC factors have also been linked to this process and discussed elsewhere [12].

Alpha thalassemia

- Alpha-Thalassemia is one of the most common haemoglobin genetic abnormalities. The primary defect is the reduced or absent production of the alpha globin chains, which constitute the moieties of several haemoglobin (Hb) types, including the adult HbA (alpha2 beta2), Fetal HbF (alpha 2 gamma 2), and the minor component HbA2 (alpha 2 delta 2). Similar to other common Globin gene disorders (i.e., beta-Thalassemia and sickle cell Anemia), alpha-Thalassemia is prevalent in tropical and subtropical world regions, where malaria was and still is epidemic, and it is thought that carriers of hemoglobinopathies are relatively protected in a malarial environment.
- One of the most prevalent genetic disorders of haemoglo bin is alpha-thalassemia.
- The main flaw is the decreased or nonexistent formation of the alpha globin chains, which are what make up the components of numerous forms of haemoglobin (Hb), such as the Alpha$_2$ beta2 for adult HbA, alpha2 gamma 2 for foetal HbF, and the HbA2 minor component (alpha 2 delta 2).
- Like other prevalent globin gene diseases (such as beta thalassemia and sickle cell anaemia), alpha thalassemia is common in tropical and subtropical regions of the world where malaria was and is currently endemic, and It is believed that Hemoglobinopathies carriers are relatively in a malarial environment, protected [13, 14].
- Alpha thalassemia has become a somewhat prevalent

clinical issue in North America, North Europe, and Australia as a result of the recent massive population migrations [15].

- It is mostly caused by deletion and less frequently by point mutations in α-Globin genes [16, 17].
- In the tropics and subtropics, carriers are present in a range of 1% to 98% of the population [18].
- It is believed that thal, which is primarily found in areas where malaria is endemic, will protect people from the severe form of the disease and its clinical sequelae [19, 20].

Different people will have different symptoms, based on which type of alpha Thalassemia is inherited. Common symptoms for each type may include:

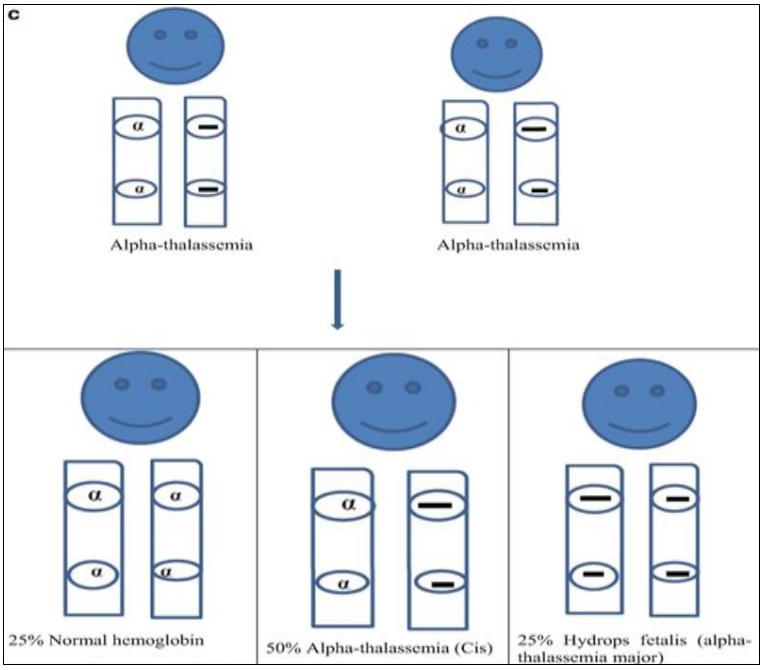

Fig 3: Alpha Thalassemia [21]

Silent alpha Thalassemia carrier: This type has no symptoms.
Alpha Thalassemia carrier: You may have mild anemia. You may have no symptoms. Or you may have mild symptoms such as mild fatigue or exercise intolerance.
Hemoglobin H disease: This type causes moderate to severe symptoms. These include lack of energy (fatigue) and exercise intolerance. You may also have an enlarged liver or spleen, yellowish skin, and leg ulcers. You have a greater risk of having a child with the most severe type, alpha thalassemia major.
Alpha thalassemia major: Babies with this type usually die before they are born.

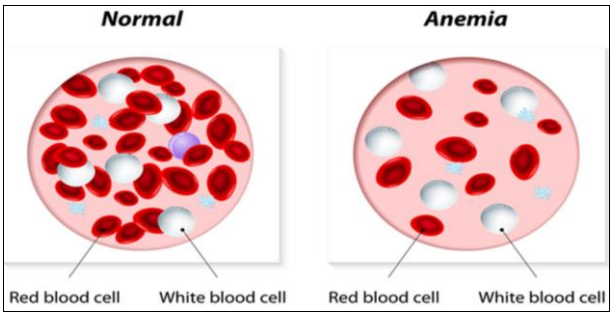

Fig 4: Thalassemia and Anemia [27]

Thalassemia and annemia

- Sickle cell Anemia's (HbSS) interactions with -Thalassemia may contribute in part to its distinctive clinical variability. Although -Thalassemia obviously impacts several hematologic characteristics of HbSS, it is unclear how the condition affects how severe the vasoocclusive system is.
- A characteristic of sickle cell anemia (HbSS) is its remarkable clinical heterogeneity [22, 23, 24, 25].
- Some patients experience recurrent vasoocclusive events on a regular basis, which can cause organ failure and dam age that can result in early death.
- Some people experience relatively few of these issues and may live a long, healthy, and productive life.
- Microcytic anaemia is frequently caused by Thalassemia trait, iron deficiency anaemia (IDA), or a combination of these. Due to poor nutritional status, IDA is a very common finding, not just in developing nations but also in the west, where women of reproductive age are frequently diagnosed with it as a result of intermittent blood loss combined with insufficient iron consumption [26].

There are many forms of Anemia, and each type has telltale symptoms. Some common types of Anemia include:

1. Iron deficiency Anemia
2. Vitamin B12 deficiency Anemia
3. Aplastic Anemia
4. Hemolytic Anemia

Thalassemia and genetics

- β Globin is encoded by a structural gene found in a cluster with the other β-like genes on chromosome 11 (11p 15.15) [28].
- The clinical presentation is widely variable because the amount of unbound α-Globin chains can be modified by both the capacity to produce α-globin chains (HBA genes variants) and the capacity to produce γ-Globin chains (HBG2 gene modulators) that can bind available α-

Globin chains to form effective Fetal Hemoglobin (HBF) [28, 30].

- The severity of HBB gene mutations and abnormalities in the HBA genes were the first factors to be identified as influencing -Thalassemia phenotypic variability

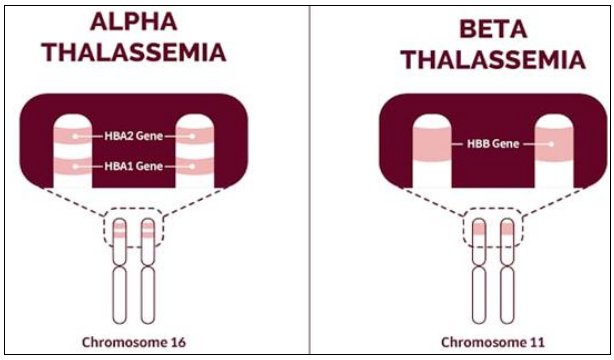

Fig 5: Thalassemia and Genetics [29]

Thalassemia in children

- Due to the high expense of therapy, which includes frequent hospital stays, iron chelation, routine transfusions, and general medical monitoring, Thalassemia is a serious health concern for both patients and their families as well as for each nation's public health system [31, 32].
- Though the etiology of depression in children and adolescents is not well understood compared to adults, however it is considered as a result of interaction between different factors. The main factors involved in the onset of depression are stressful events (chronic illness), family-related factors (death in the family, divorce, physical abuse, intra-family conflicts or economic difficulties that undermine the quality of the relation within family) or social factors (peer group or school when children experience it as "pressure").
- Since childhood is generally regarded as a time of joy without signs of sorrow, the idea of depression during this time has been controversial. This point of view makes it clear that depression in children continues to go undetected and, as a result, mistreated.

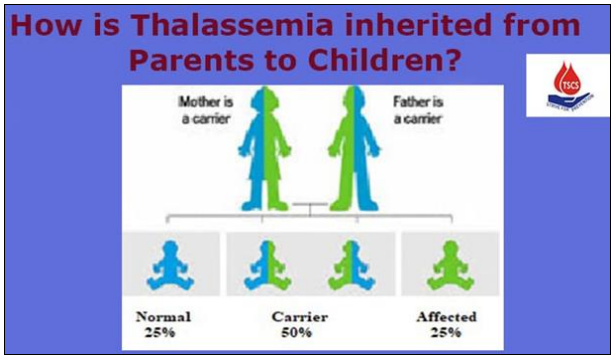

Fig 6: Thalassemia in Children [33]

Thalassemia in pregnancy

- During pregnancy, a woman carries one or more living ch ildren as a result of the implantation of egg.
- Throughout gestation, the fertilised zygote remains in the uterus.
- During pregnancy, a number of physiological changes tak e place.
- The coagulation system and haematological system under go significant alterations throughout a typical pregnancy. [34].
- Healthy pregnancy outcomes have become the expectation
- In women with Thalassemia and provided that a multidisciplinary team is available, gestation can be completely safe for both mother and child However, pregnancy in Thalassemia should be considered high risk and should always be preceded by a complete preconception assessment. In patients with severe myocardial or liver iron overload.
- Conception should be delayed until after a period of intensive chelation. During pregnancy, a close follow-up of maternal disorders, as well as that of Fetus status, is recommended.
- Most people with non-trans fusion dependent thalassemia appear to be safe to become pregnant, although larger and more thorough investigations are required [35].

Symptoms

There are numerous Thalassemia symptoms. The following are some of the most typical:

- Bone malformations,
- Particularly in the face
- Black urine slowed development and growth excessive weariness
- Pale skin

The signs and symptoms of Thalassemia are not always obvious. The illness also has a tendency to manifest its symptoms later in childhood or adolescence [36].

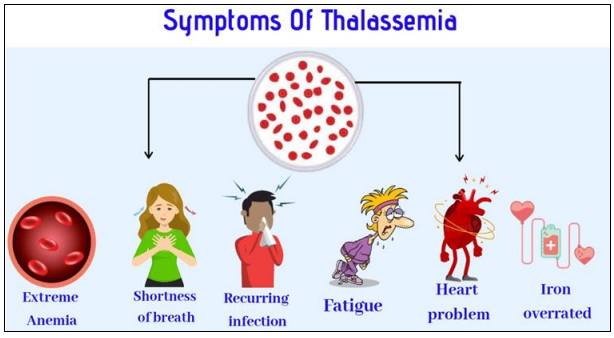

Fig 7: Symptoms of Thalassemia [37]

Causes

- In blood cells, the protein haemoglobin carries oxygen throughout the body. Hemoglobin is made in the bone marrow using iron from the diet [38].
- Thalassemia is caused by mutations in the DNA of cells that make hemoglobin the substance in red blood cells that carries oxygen throughout your body. The mutations associated with thalassemia are passed from parents to children
- Hemoglobin molecules are made of chains called alpha and beta chains that can be affected by mutations. In thalassemia, the production of either the alpha or beta chains are reduced, resulting in either alpha-thalassemia or beta-thalassemia.
- In alpha-thalassemia, the severity of thalassemia you have depends on the number of gene mutations you inherit from your parents. The more mutated genes, the more severe your thalassemia.
- In beta-thalassemia, the severity of thalassemia you have depends on which part of the haemoglobin molecule is affected.

Diagnosis

- Moderate and severe Thalassemia are often diagnosed in childhood because symptoms usually appear within the first two years of your child's life [39].
- Thalassemia is indicated by red blood cells with abnormal shapes. The haemoglobin electrophoresis test may also be carried out by the lab technician. By separating the various molecules in the red blood cells, this test enables them to recognise the abnormal type [36].

Treatment

- The treatment for Thalassemia depends on the type and severity of disease involved. Your doctor will give you a course of treatment that will work best for your particular case.

Some of the treatments include

- Chelation therapy
- Blood transfusions
- Steam cell transplant
- Bone marrow transplant
- Medications and supplements
- Possible surgery to remove the spleen or gallbladder

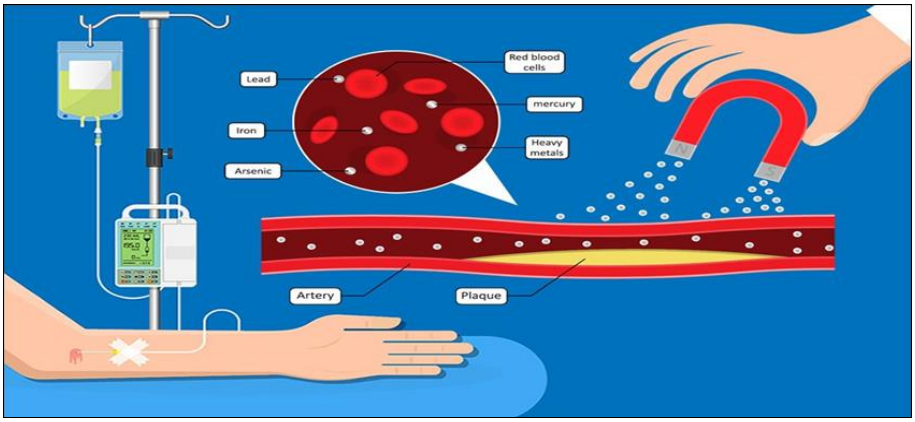

Fig 8: Chelation Therapy [44]

Chelation therapy

- In cases of ongoing transfusion therapy, with each RBC unit containing ~ 200 mg of iron, cumulative iron burden is an inevitable consequence. In TI and TM patients, the rate of Transfusional and GI tract iron accumulation is generally 0.3-0.6 mg/kg per day [40].
- Severe anaemia and IE, which inhibit the production of Hepcidin, a protein that regulates iron absorption from the GI tract and boosts the release of recycled iron from macrophages, can lead to increased GI tract iron absorption [41, 42, 43].
- Parents are provided information by physicians about the currently available iron chelators, and together they make an informed decision about the chelator of choice for the child.
- The initial recommended dose is 30-40 mg/kg per day for daily use 5-7 days each week in regularly transfused Thalassemia patients. Chelation generally begins between 2 and 4 years of age, after 20-25 RBC units are transfused, with a serum Ferritin level > 1000 µg/dL
- The overall aim of Chelation therapy is to maintain a "safe" iron status at all times. Ideally, Chelation therapy should be administered to prevent iron accumulation and iron-related complications including hepatic, Endocrinological and cardiac dysfunction. There is evidence showing that the age at which iron Chelation is started in patients with Thalassaemia major is a key factor in their survival [45, 46, 47].

Blood transfusions

Iranian Blood Transfusion Organization (IBTO) is the only nationally accredited organization in Iran that performs blood transfusion procedures ranging from blood donor recruitment as well as blood distribution.

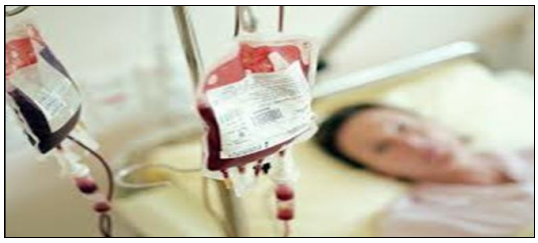

Fig 9: Blood Transfusion [49]

Goals of blood transfusion therapy

- Appropriate goals of transfusion therapy and optimal safety of transfused blood are the key concepts in the protocol for routine administration of red blood cells to patients with Thalassaemia.

The major goals are

- Use of donor erythrocytes with an optimal recovery and half-life in the recipient.
- Achievement of appropriate haemoglobin level.
- Avoidance of adverse reactions, including transmission of infectious agents [48].

Steam cell transplant

- Also called a bone marrow transplant, a stem cell transplant might be an option in some cases. For children with severe Thalassemia, it can eliminate the need for lifelong blood transfusions and drugs to control iron overload.
- This procedure involves receiving infusions of stem cells from a compatible donor, usually a sibling [50].
- The large majority of transplants in Thalassemia have been performed using bone marrow derived stem cells. In the EBMT survey, more than 80% of the transplants have been performed using bone marrow derived cells. Bone marrow derived stem cells continue to be the preferred source of stem cells for transplantation in Thalassemia

even in the most recent years.

- In 2003, Locatelli first successfully proposed the use of identical sibling cord blood derived Hemopoietic stem cells for transplantation in Thalassemia [51].

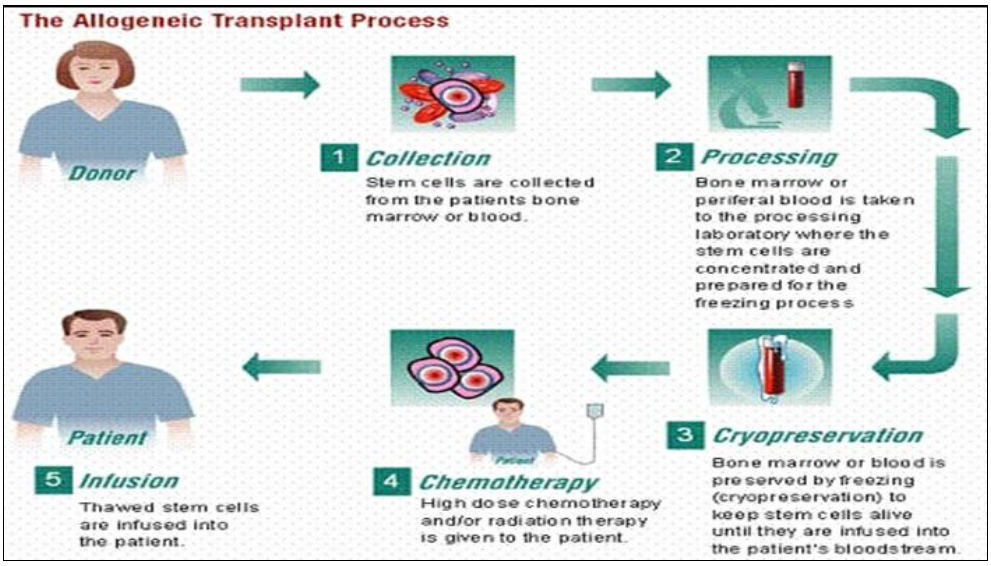

Fig 10: Steam cell transplant [52]

Herbs used in thalassemia

- Herbs help in getting rid of Thalassemia symptoms naturally. Herbal remedies are safe and may be taken on a regular basis. Herbs help to boost up the immunity. Herbs also reduce weakness and help to get rid of recurrent infection. Herbal remedies help in the formation of healthy RBCs.
- Stem cells are the mother cells that are responsible for developing an entire human body from a tiny two celled embryo; due to their unlimited divisions and strong power to differentiate into all the cells of different lineage. This power of stem cells has been harnessed to isolate them outside the human body, concentrate in the clean environment and implant back. Thus, stem cell treatment involves administration of concentrated cells in the targeted area to form colonies; a characteristic of stem cells, adapt the properties of resident stem cells and initiate some of the lost functions that have been compromised due to disease or injury [53].
- Researchers have recently discovered herbal treatments for -Hemoglobinopathies, such as sickle cell disease (SCD) and -Thalassemia that may be effective. In human leukemic K562 cells, the Bergatene-Containing extract of Aegle Marmelos promoted erythroid development and HbF induction [54, 55].

Kumara-Kalyana Rasa

It is a natural herbal remedy that helps to get rid of Thalassemia symptoms, formation of RBCs, boosting up the energy, getting rid of weakness, boosting the immune system and getting rid of recurrent infections. This is a herbal treatment to prevent recurrent infections in the body [56].

Pravala Pisti

This is a natural herbal solution to get rid of anemia. It helps in the formation of protein that helps in making healthy RBCs. It boosts the immune system and helps to reduce weakness in the body. It boosts the energy and improves other symptoms of thalassemia [56].

Kaharava Pisti

This is herbal remedy for the natural treatment of thalassemia. It helps in the formation of healthy RBCs. It reduces weakness and helps to get rid of other symptoms. It helps in the proper circulation of blood throughout the body [56].

Moti Pisti

This herbal remedy is a wonderful solution to prevent the symptoms of thalassemia. It may be taken regularly to help in the formation of healthy RBCs. It also helps in making healthy protein for the formation of hemoglobin. It reduces the risk of developing thalassemia. It may be taken regularly to prevent the complications of the disease [56]

Giloy Sattva

It is a useful herb that has been used traditionally for the treatment of any kind of blood disorders. It helps to get rid of anemia and makes the body healthy. It helps in the formation of RBCs. It increases the blood supply to all parts of the body and helps in the normal functioning of all the body organs [56].

Pravala Pancamrta

It is an herbal remedy to get rid of thalassemia. It promotes healthy functioning of the body. It helps in the formation of RBCs and also produces protein [56].

Fig 11: Herbal drugs used in Thalassemia [57]

Conclusion

The Thalassemia are relatively common diseases. Genetic counselling is paramount, and may even decrease the incidence of the more serious conditions. Most children tolerate the anemia quite well and do not require any interventions. Thalassemia minor will never go away; people

who think they have thalassemia minor or are at risk should have blood test so in future they can be aware for themselves in terms of not having a thalassemia major child. Also by having blood test will help the community so that, exact number of people who carry thalassemia minor can be assessed. Thalassemia major can be cured by bone marrow transplantation but, rarely will it successes.

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