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Review Article

Phytocompounds Targeting For The Treatment Of β -Thalassemia: A Review

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ABSTRACT

For treating β -thalassemia, increasing foetal haemoglobin (HbF) production with drugs shows promising result. Many studies have focused on finding new HbF-inducing phytocompounds and understanding how they work. This review compiles the identified agents so far. While these agents can stimulate HbF production, chemotherapy drugs cannot be practically used for treating β -haemoglobinopathies, like β -thalassemia, due to their toxicity and growth-inhibiting effects. To overcome this issue, researchers are exploring natural plant sources for effective, safe, and easy-to-use HbF-inducing agents. This review highlights summarizes the natural phytocompounds that stimulate HbF production, aiming to provide new insights into future treatments for β -thalassemia.

INTRODUCTION

Thalassemia, the most common form of hereditary anaemia [Cao & Galanello, 2010], is a genetic disorder that results from the impaired synthesis of one of the two globin chains in haemoglobin [Angastiniotis et al., 2019]. Haemoglobin, the protein in red blood cells responsible for carrying O₂ throughout the body, is composed of two types of protein chains: α -globin and β -globin [Marengo-Rowe, 2006]. So, the thalassemia can be classified into two main types based on which globin chain is affected: α -thalassemia and β -thalassemia [Shafique et al., 2021]. Genetic

disorders caused by mutations in the β -globin gene are widely known as the human β -haemoglobinopathies [Hariharan et al., 2021], in which β -thalassemia is the most prevalent ones, particularly in the Mediterranean, Africa, and Southeast Asia, leading to great mortality and morbidity [Ng et al., 2014; Weatherall & J, 2010]. The high occurrence of β -thalassemia mutations is due to the reason that causes a mild severity of malarial infection in the heterozygous state. However, in the homozygous state, these mutations shorten the lives of affected individuals [Flint et al., 1998]. β -thalassemia is caused by

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inherited mutations in the HBB gene complex [Higgs et al., 2012], resulting in a total absence or severe decrease in the production of β -globin chains. Completely absence of β -chain causes β^0 -thalassemia or thalassemia major. Reduced amounts of detectable beta globin cause β^+ -thalassemia or thalassemia intermedia [Thein, 2013]. But in α -thalassemia, there resulting in the decreased production of α -globin chain. The lack of β -globin chain production leads to the accumulation and precipitation of free intracellular α -globin chains, which consequently result in premature haemolysis of red blood cells and apoptosis of erythroid precursors [El-Beshlawy et al., 2009; Schrier, 2002]. Ineffective erythropoiesis has also been known to be related to inefficient iron utilization [Rivella, 2009]. Therefore, the combined effects of ineffective erythropoiesis, haemolysis, and hypersplenism are the main culprits of severe anaemia in β -thalassemia patients [Mabaera et al., 2008]. The β -globin gene mutations can vary widely, leading to different forms and severities of β -thalassemia. The most severe form, β -thalassemia major, often requires regular blood transfusions and iron chelation therapy to manage iron overload due to transfusions [Ali et al., 2021]. Without treatment, patients with β -thalassemia major may suffer from severe anaemia, growth retardation, skeletal abnormalities, and other complications [Bajwa & Basit, 2023]. Intermediate forms, such as β -thalassemia intermedia, have a variable clinical presentation and may require intermittent transfusions and supportive care. The clinical management of β -haemoglobinopathies involves various strategies to alleviate symptoms and prevent complications [Kohne, 2011]. The mainstay of treatment for β -thalassemia includes regular blood transfusions to maintain adequate haemoglobin levels and prevent severe anaemia. However, long-term transfusion therapy may cause iron overload from the gradual breakdown

of transfused blood, potentially resulting in cardiac failure and/or death [Mabaera et al., 2008; Lal et al., 2021]. Advances in iron chelation therapy, which involves the use of medications to remove excess iron, have improved survival rates, but the effectiveness of treatment depends on adherence to iron chelation regimens [Mobarra et al., 2016]. Allogeneic hematopoietic stem cell transplantation (HSCT) is one of the gene transfer therapies aimed at addressing the underlying molecular causes of β -haemoglobinopathies. Several hundred thalassemia patients have successfully undergone HSCT with promising results [Bhatia & Walters, 2008].

However, HSCT is limited to a small proportion of haemoglobinopathy patients due to the requirement for matched sibling donors and the risk of complications [Bhatia & Walters, 2008], such as graft-versus-host disease. Younger patients and those without significant disease complications tend to have the best outcomes following HSCT. Transferring γ - or β -hematopoietic stem cells from patients can be another therapy option for β -thalassemia patients. Clinical gene transfer protocols have taken a long time to be approved, as the transduction of human hematopoietic stem cells and gene expression must reach high efficiency and levels [Srivastava & Shaji, 2017; Sadelain, 2006]. Although this approach has successfully passed initial human trials, issues such as low autopolydomy recombination, insertional mutagenesis, and the effects of inserted vectors on the expression of nearby genes could potentially limit its application [Dunbar et al., 2007; Hargrove et al., 2008]. Apart from gene therapy, reactivating HbF through chemical agents also appears promising enough to develop into effective interventions to cure human β -haemoglobinopathies [El-Beshlawy et al., 2009]. Studies have revealed that homozygous β -thalassemia patients do not suffer severe anaemia until foetal γ -globin genes are silenced, and

patients with hereditary persistence of foetal haemoglobin (HPFH), where HbF persists at high levels into adulthood, only suffer mild anaemia [Bianchi et al., 2009; Forget, 1998; Gallo et al., 1979]. Therefore, increasing the synthesis of HbF by reactivating foetal γ -globin genes is a potential therapy for patients suffering from β -thalassemia. Pharmacological induction of HbF can correct the globin chain imbalance in β -thalassemia patients. Efforts have been made to identify naturally occurring inducers and drug treatments that can increase HbF synthesis and promote the expression of foetal γ -globin genes [Bou-Fakhredin et al., 2022; Olivieri et al., 1998]. Chemotherapeutic agents such as 5-azacytidine and hydroxyurea (HU) have been reported to enhance HbF production. However, these agents exhibit low efficacy and specificity, myelotoxicity, and carcinogenicity, as well as modest responses to treatment, greatly limiting their usefulness in clinical practice [Li et al., 2011; Watanapokasin et al., 2005; Heller et al., 1984]. The limitations of current treatments and the complex nature of β -haemoglobinopathies necessitate continued research and development of new therapeutic strategies [Fрати & Miccio, 2021]. Discovering novel screening platforms for identifying potential HbF inducers with high efficiency and accuracy is essential. Additionally, identifying new HbF-inducing agents from natural sources that combine efficacy, safety, and ease of use is a high priority [Mabaera et al., 2008]. Advances in genetic engineering and gene editing technologies, such as CRISPR-Cas9, offer new avenues for treating β -haemoglobinopathies by directly correcting the genetic mutations responsible for the diseases. These technologies have the potential to provide long-lasting and possibly curative treatments, but challenges such as delivery methods, off-target effects, and regulatory hurdles need to be addressed [Lu et al., 2023; Papizan et al., 2020]. Research into the

molecular mechanisms regulating HbF expression and the development of more effective and safer HbF inducers is ongoing. Understanding the genetic and epigenetic factors (EF) involved in the switch from foetal to adult haemoglobin production can lead to new therapeutic targets. Combination therapies that include HbF inducers, gene editing, and supportive care may offer the best outcomes for patients with β -haemoglobinopathies [Sankaran, et al., 2013].

EPIDEMIOLOGY

From 2006 to 2018, the number of thalassemia patients increased from 354 to 1577, with the prevalence rate rising from 0.74 to 2.76 per 100,000 persons. Patients were categorized into α -thalassemia or β -thalassemia. Female prevalence consistently surpassed male prevalence [Lee et al., 2006-2018] (female-to-male ratio: 1.70–2.00). Incidence rates decreased from 0.24 in 2006 to 0.15 per 100,000 persons in 2011 but rose to 0.41 by 2018, doubling in the last two years of the study [Lee et al., 2006-2018]. Incidence rates were higher in women and peaked in age groups 0–9, 30–39, and over 70 years. Blood transfusions were received by 27.7% of patients, with the annual rate decreasing from 34.7% in 2006 to 20.6% in 2018. Transfusion patients had higher incidences of comorbidities, significantly associated with transfusion events [Kadhim et al., 2017; Cunningham et al., 2004] (e.g., diabetes). A total of 23 studies reported population-based estimates of β -thalassemia. The data came from several regions around the world (Figure 1):

North America:

This included studies from the United States (US) and combined data from the US and Canada [Xie et al., 2018].

Europe:

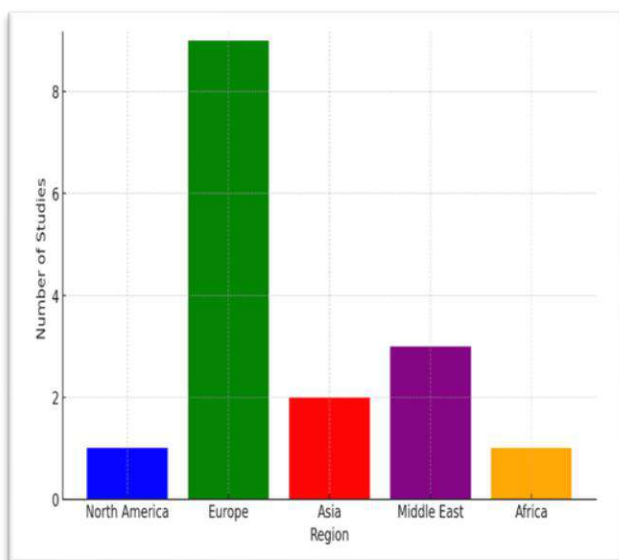
Countries included were Denmark, England, France, Germany, Greece, Italy, the Netherlands, Spain, and the United Kingdom (UK) [Hansen et



al., 2020; Kleinman et al., 2018; Voskaridou et al., 2019].

Asia:

Studies were conducted in Malaysia and Taiwan [Mohd Ibrahim et al., 2020; Tang et al., 2021].

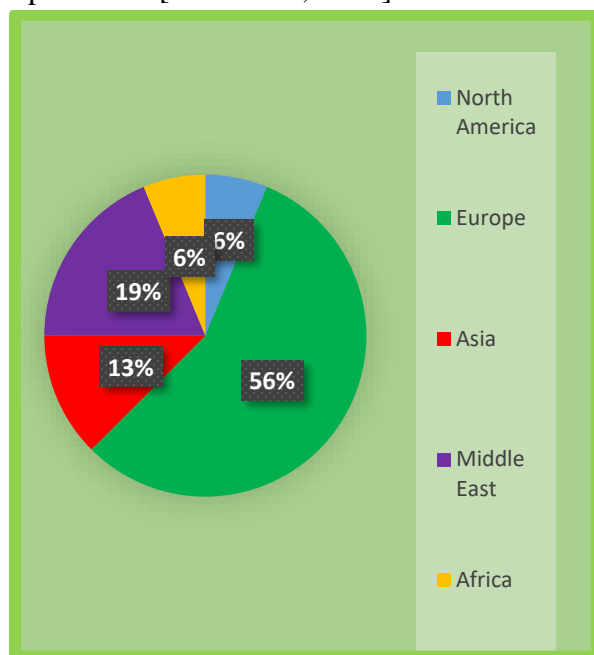


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Middle East:

Countries included Oman, Iran, and Iraq [Rajab et al., 2000; Hadipour et al., 2019].

Africa: Only one country, Algeria, was represented [Grifi et al., 2018].



B

Figure 1:

A. The bar plot showing the number of studies reporting population-based estimates of β -thalassemia by region.

B. Pie chart presentation of the plot (Sporce- Lee et al., 2006-2018).

For a few countries, multiple studies were found that reported β -thalassemia prevalence, showing moderate variations in estimates (as shown in Figure 2):

United States (US):

The prevalence ranged from 0.2 per 100,000 people for the period 2004–2008 (using a stringent case definition) [Hulihanet al., 2015] to 0.8 per 100,000 people in 2016 (based on International Classification of Diseases, Ninth Revision [ICD-9] codes) [Paramore et al., 2017].

England: Estimates varied from 1.1 per 100,000 people for the period 2009–2018 (based on International Classification of Diseases, Tenth Revision [ICD-10] codes) [Jobanputra et al., 2020]

to 2.3 per 100,000 people for the period 2019–2020 (based on the National Haemoglobinopathy Registry (NHR) Annual Data Report 2019/20).

France:

The prevalence was reported as 0.6 per 100,000 people for the period 2005–2008 and 0.8 per 100,000 people in 2019 (based on the French National Registry (FNR) of thalassemia patients) [Thuret et al., 2010; Agouti et al., 2019].

Iran:

Estimates ranged from 23.2 per 100,000 people in 2015 [Kadhim et al., 2017] to 32.6 per 100,000 people for the period 1955–2018 in the Fars Province [Haghpanah et al., 2021].

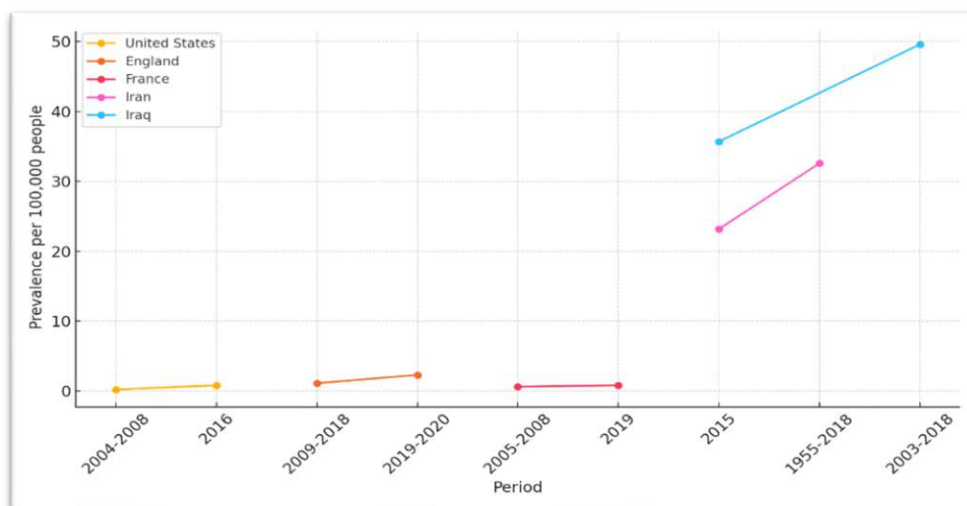


Figure2: This plot showing the prevalence of the condition in different countries over specified periods (Source- Hulihalet al., 2015; Kattamis et al., 2020)

Inheritance Pattern

Thalassemia major and thalassemia intermedia are inherited in an autosomal recessive pattern [Angastiniotis et al., 2019]. This means that for an individual to be affected by these forms of thalassemia, they must inherit two altered copies of the HBB gene, one from each parent. So, when both copies of the HBB gene in each cell have variants, the production of haemoglobin is affected, leading to the severe symptoms observed in thalassemia major and intermedia [Gulani, & Weiler, 2023] (as shown in Figure 3). The HBB gene provides instructions for making a part of

haemoglobin [Morton et al., 1984], which is the protein in red blood cells that carries oxygen throughout the body [Gell, 2018]. Parents of a child with an autosomal recessive condition such as thalassemia major or intermedia typically carry one altered copy of the HBB gene and one normal copy (Figure 3). These carriers, also known as heterozygotes, do not usually show any signs and symptoms of thalassemia [Langer, 2024]. This is because the presence of one normal HBB gene is sufficient to produce enough haemoglobin for normal function.

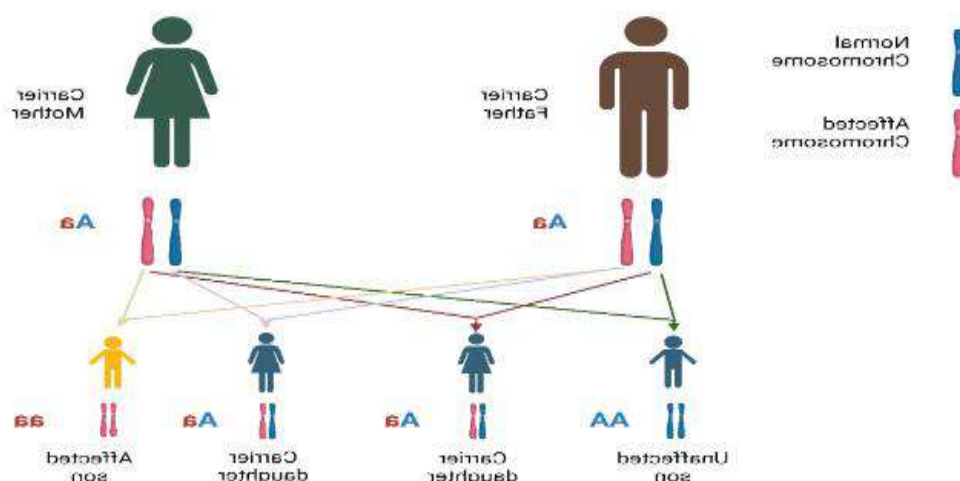


Figure3: The autosomal recessive pattern of inheritance where both parents of an individual carry one altered copy of gene. (Source- <https://app.biorender.com/> ; data from Angastiniotis et al., 2019)

Etiology

As mentioned above, β -thalassemia is an inherited blood disorder caused by various mutations-over 200 disease-causing mutations have been identified or, in rare cases, deletions of the beta-globin gene (HBB) located on chromosome 11

[Cao et al., 2010]. Most of these mutations are point mutations [Treisman et al., 1983] that disrupt the normal processes of transcriptional control, translation, and splicing of the HBB gene and its product (Figure 4).

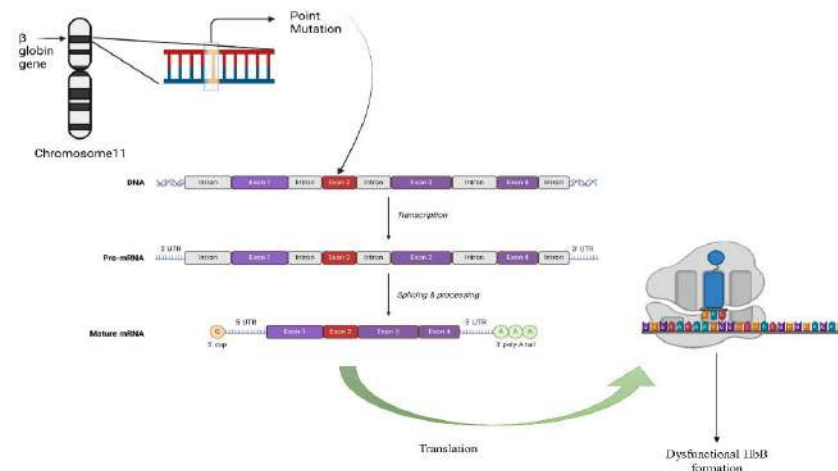
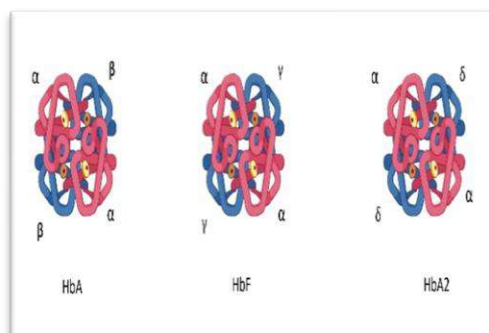


Figure 4: Point mutations that disrupt the normal processes of transcriptional control, translation, and splicing of the HBB gene. (Source- <https://app.biorender.com/> ; data from Thein, 2023)

The severity of the disease is influenced by the bi-allelic inheritance of two copies of the beta-globin gene, one on each chromosome 11, and by the diversity of the disease-causing mutations. The genotypic variability in beta-globin synthesis is categorized into two types: β^+ for decreased production of beta-globin and β^0 for complete absence of beta-globin production [Needs et al., 2023]. The phenotypic expression of β -thalassemia varies and is classified into three types based on the severity: minor, intermedia, and major [Langer, 2024]. β -thalassemia minor occurs when an individual is heterozygous [Galanello & Origa, 2010], having one unaffected beta-globin gene and one affected gene, either β^+ or β^0 . β -thalassemia intermedia and major occur in individuals who are either homozygous (having two affected β -globin genes) or compound heterozygous (having one β^+ and one β^0 gene) [Needs et al., 2023;].

Pathophysiology

Variation in the HBB gene cause beta thalassemia by affecting the production of beta-globin (as shown in Figure 5), a component of haemoglobin [Saad et al., 2023]. HbF is the primary haemoglobin until six months of age and consists of two alpha chains and two gamma chains [Kaufman et al., 2023]. Adult haemoglobin primarily consists of haemoglobin A (HbA), with two alpha chains and two beta chains, and a smaller amount of haemoglobin A2 (HbA2), with two alpha chains and two delta chains [Marengo-Rowe, 2006] (Figure 6).



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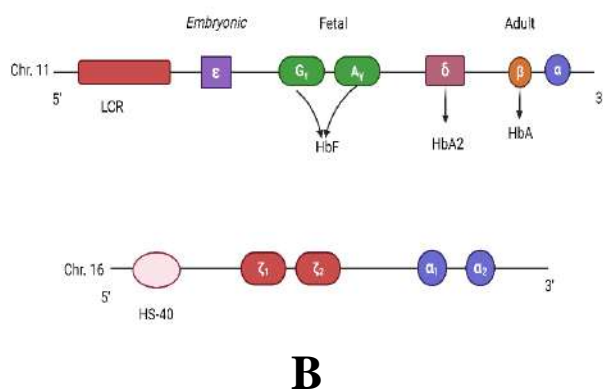


Figure 6: A) Different types of haemoglobin. HbA, HbF, HbA2 with their globin chains. B) Schematic diagram of α - and β -globin gene clusters and the types of haemoglobin produced at each developmental stage. (Source-<https://app.biorender.com/>; data from Needs et al., 2023)

β -thalassemia has two main pathological mechanisms: decreased haemoglobin synthesis leading to anaemia and increased HbF and HbA2 levels due to reduced beta chains for HbA formation, and excess α -chains forming insoluble inclusions [Needs et al., 2023] that cause significant intramedullary haemolysis (Figure 5). This ineffective erythropoiesis results in severe anaemia, erythroid hyperplasia, bone marrow expansion, and extramedullary haematopoiesis, leading to bony deformities like frontal bossing and maxillary protrusion [Nienhuis et al., 2012]. Bone marrow expansion signals through the bone morphogenetic protein (BMP) pathway, inhibiting hepcidin production and causing iron hyperabsorption. Inadequately treated or transfusion-dependent patients risk iron overload, which can damage organs [Xiao et al., 2020; Nemeth et al., 2023]. Hepatosplenomegaly from extramedullary haematopoiesis and ongoing haemolysis can cause thrombocytopenia and hepatic dysfunction [Murakami et al., 2013].

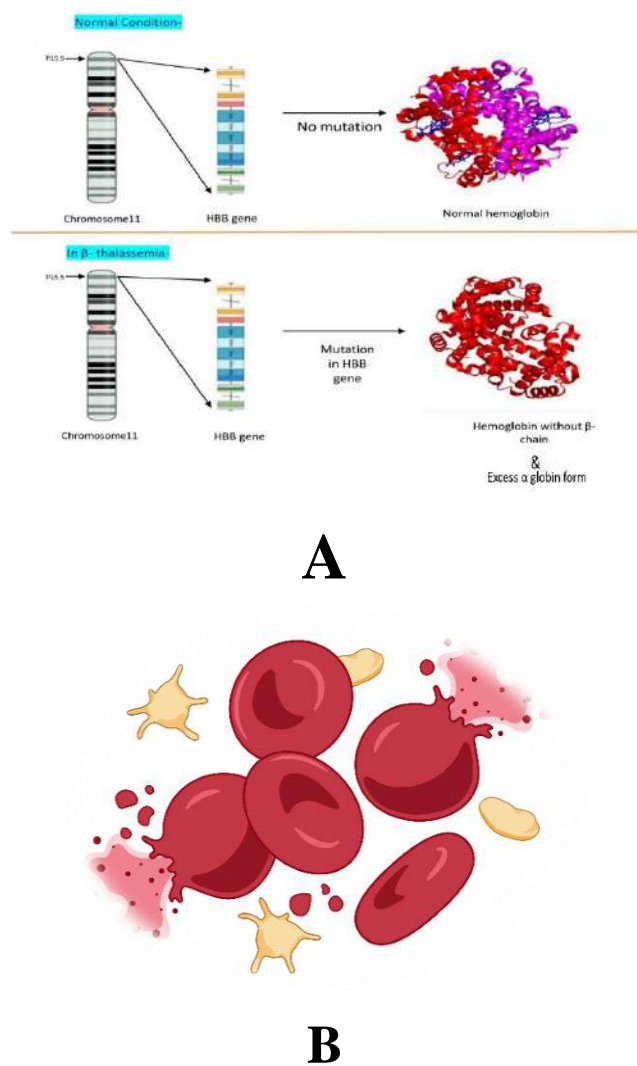


Figure 5: A) Comparison between haemoglobin formation in normal condition and in β -thalassemia with free α chain. B) Haemolysis of RBC. (Source-<https://app.biorender.com/>; data from Needs et al., 2023)

Review of the literature

Individuals with elevated HbF levels experience milder symptoms and have a normal life expectancy. Consequently, increasing HbF levels has proven to be a successful treatment strategy for β -thalassemia patients [Bianchi et al., 2009]. However, iron overload remains the primary cause of death in those with β -thalassemia [The Lancet, 2018; Taher et al., 2017]. In patients with β -thalassemia, the presence of faulty β -globin molecules can be counteracted by the production

of γ -globin, a molecule similar to β -globin. γ -globin can pair with α -globin chains to create HbF [Ng et al., 2014]. By boosting γ -globin production, the imbalance between α and β chains is reduced, leading to less haemolysis, more effective red blood cell production, and an overall increase in total haemoglobin levels. So according to Gambari et al., 2007 there are several HbF inducing agents such as Hydroxyurea (HU), 5-Azacytidine (5-Aza), Decitabine, Citarabine [Bianchi et al., 2009], Rapamycin, Thalidomide, Revlimid, Pomalidomide have been discovered that results in boosting γ -globin production [El-Beshlawy et al., 2009; Perrine et al., 2005; Fibach et al., 2006; Aerbajinai et al., 2007; Mabaera et al., 2008], that reduce the imbalance between α and β chains, leading to less haemolysis.

HbF Inducers act via P38 MAPK Signalling Pathway

From the above information, thalidomide, pomalidomide, hydroxyurea (HU), decitabine, show high potential in inducing HbF expression [Rahim et al., 2013]. Thalidomide, an immunomodulator, significantly increases HbF levels and erythroid precursor proliferation by activating the P38MAPK signalling pathway and

Reactive Oxygen Species (ROS) [Aerbajinai et al., 2007]. Sodium butyrate, a histone deacetylase (HDAC) inhibitor, also activates the P38MAPK pathway and guanylate cyclase, leading to γ -globin gene induction and epigenetic changes [Dehghanifard et al., 2012; Fathallah et al., 2008; Kodeboyina et al., 2010]. It enhances acetylation of H4 histone and triggers pathways involving C-myc, C-myb, and boosting erythroid precursor proliferation [Boosalis et al., 2001]. Other HDAC inhibitors like trichostatin and apicidin similarly induce γ -globin gene expression through the P38MAPK pathway [Sangerman et al., 2006]. Decitabine and 5-azacytidine, acts as DNA methylation inhibitors, demethylate the γ -globin promoter, activating this gene in adult erythroid cells [Kiefer et al., 2008]. HU, a cytotoxic drug, increases HbF levels and promotes the production of foetal-like cells in β -thalassemia patients by inducing erythroid differentiation and activating the cGMP/soluble guanylate cyclase (sGC)/PKG pathway [Fathallah & Atweh, 2006; Ikuta et al., 2001]. HU and butyrate also stimulate HbF production via the cAMP pathway and small GTP-binding proteins [Keefer et al., 2006; Tang et al., 2005].

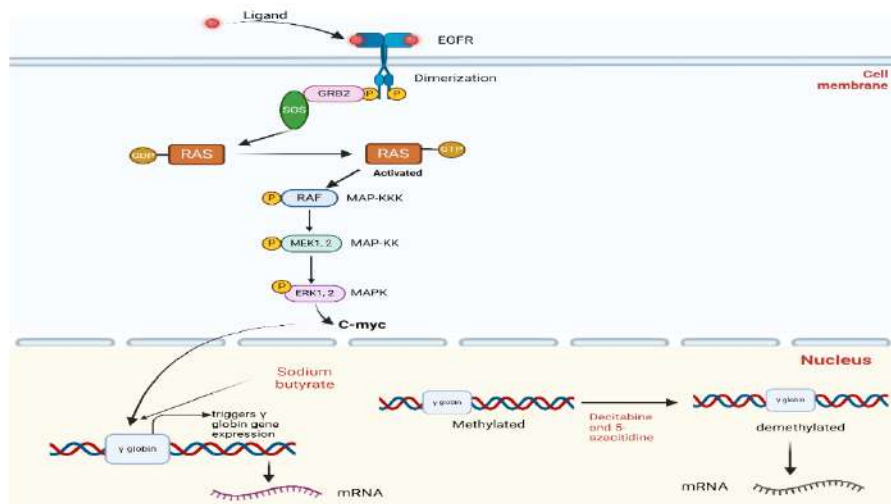


Figure 7: HbF Inducing drugs act via P38 MAPK Signalling Pathway that triggers the γ -globin gene expression. (Source- <https://app.biorender.com/> ; data from Rahim et al., 2013)

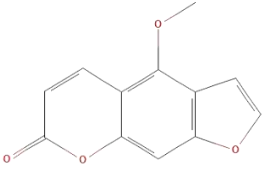
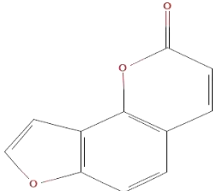
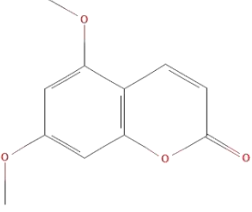
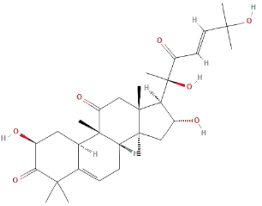
Phytocompounds as HbF Inducer

In recent years, scientists have undertaken extensive research to discover phytocompounds

treatments that might be effective for β -haemoglobinopathies, such as β -thalassemia (listed in Table 2). An extract from the *Aegle marmelos* plant, which contains a compound called bergaptene, has been shown to trigger the differentiation of erythroid cells and stimulate the production of HbF in human leukemic K562 cells [Li et al., 2011; Guerrini et al., 2009; Lampronti et al., 2003]. Angelicin, a compound present in the fruit of *Angelica archangelica*, has been shown to be highly effective in promoting the differentiation of erythroid cells. Research indicates that angelicin significantly boosts the synthesis of HbF in erythroid progenitor cells and increases the accumulation of γ -globin mRNA in human leukemia K562 cells [El-Beshlawy et al., 2009; Lampronti et al., 2003]. Citropten found in

bergamot juice, hold significant roles in the realm of human health. They possess the remarkable ability to stimulate the process of erythroid differentiation, the expression of the γ -globin gene, and the synthesis of HbF in human erythroid cells [Guerrini et al., 2009]. These actions are particularly noteworthy as they offer potential therapeutic avenues for addressing β -thalassemia. Cucurbitacin D (CuD), a compound found in the Chinese medicinal herb *Fructus trichosanthis*, has been shown to be more effective than hydroxyurea in inducing HbF production. Research indicates that CuD not only increases the percentage of foetal cells but also enhances the HbF content in K562 cells, a type of human leukemia cell line, while exhibiting significantly lower cytotoxicity [Liu et al., 2010; Li et al., 2011].

Table 2: HbF inducing natural remedies or Phytocompounds.

Phytocompounds	Plant Source	Biological effect
 Bergaptene	<i>Aegle marmelos</i>	Erythroid differentiation of K562 cells, HbF induction [Li et al., 2011; Guerrini et al., 2009].
 Angelicin	<i>Angelica archangelica</i>	Erythroid differentiation, HbF induction [El-Beshlawy et al., 2009; Lampronti et al., 2003].
 Citropten	Bergamot orange	Erythroid differentiation and HbF production [Guerrini et al., 2009].
 Cucurbitacin D	<i>Fructus trichosanthis</i>	Enhances the HbF content in K562 cells, a type of human leukemia cell line, while exhibiting significantly lower cytotoxicity [Liu et al., 2010; Li et al., 2011].

Cucurbitacin D		
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This review highlights another natural compounds that derived from plants and show promise in the treatment of β -thalassemia. Specifically, these plant-based compounds have demonstrated the key therapeutic effects: it helps increase the levels of HbF through demethylate the γ -globin promoter and also activates the P38 MAPK pathway, leading to γ -globin gene induction and other epigenetic changes. Nuamsee et al., 2021 on their “Trienone analogs of curcuminoids induce fetal hemoglobin synthesis via demethylation at γ -globin gene promoter” literature reported that natural “curcuminoids”—curcumin, demethoxycurcumin (DMC), and bis-demethoxycurcumin (BDMC)- induce HbF production in erythroid progenitors. This study explores whether trienone analogs of these curcuminoids can induce HbF in K562 erythroleukemic cell lines and primary human erythroid progenitor cells from β -thalassemia/HbE patients. According to Zhu et al., 2020 it has been reported that “Sulforaphane”, found in cruciferous vegetables like broccoli, can activate the p38 MAPK pathway and has been shown to impact gene expression via epigenetic mechanisms.

FUTURE PERSPECTIVE

Given the lack of effective HbF-inducing agents for β -thalassemia treatment, researchers are exploring natural herbal medicines as potential alternatives. YiSui ShenXu Granule (YSSXG), a blend of 11 herbs, has been used for over 20 years to treat β -thalassemia [Zhang et al., 2008; et al., 2006]. A recent randomized single-blind trial confirmed its clinical efficacy, showing improvement in liver and spleen conditions without adverse reactions. The mechanism likely involves in demethylate the γ -globin gene to increase HbF production, compensating for the β -globin gene deficiency [Wu et al., 2007; Fang et

al., 2007]. Additionally, Nuamsee et al., 2021 & Zhu et al., 2020 reported that curcuminoids (CUR) extract from *Curcuma longa* L and Sulforaphane from *Brassica oleracea* can induce HbF synthesis by activating p38 MAPK and gene expression via epigenetic changes. From the above information, CUR and Sulforaphane require further in vivo toxicity testing and clinical evaluation for therapeutic treatment of β -thalassemia in future. Overall, natural herbal medicines show high potential for HbF induction with lower cytotoxicity compared to traditional chemotherapeutic agents, although further research is needed to ensure their safety and efficacy for clinical use.

CONCLUSION:

β -thalassemia is a genetic blood disorder characterized by reduced production of haemoglobin. Current treatments for β -thalassemia have notable limitations. One promising approach is the induction of HbF using natural agents. Research indicates that various natural substances, such as angelicin, rapamycin, curcuminoid, citropten, and bergaptene, can increase HbF levels in β -thalassemia patients. Another critical goal in managing β -thalassemia is reducing iron overload. Due to their lack of side effects, natural agents warrant further investigation to understand their biological activity better. Identifying the most effective natural therapeutic agents to boost HbF production and decrease iron overload could significantly improve patient outcomes. Additionally, more research is needed to determine the bioavailability and impact of these natural compounds on humans. Traditional chemotherapeutic agents, including 5-azacytidine, hydroxyurea, rapamycin, thalidomide, revlimid, pomalidomide have been used to stimulate HbF synthesis in β -thalassemia

patients. However, their use is limited by side effects such as cytotoxicity, growth inhibition, potential long-term carcinogenicity, and only moderate effectiveness in inducing HbF. With advancements in biotechnology, more research is expected to optimize new treatments and natural remedies to reactivate HbF synthesis in β -thalassemia patients. Future studies should focus on discovering additional HbF-inducing agents from natural sources and traditional medicines worldwide. Extensive research is necessary to evaluate the efficacy and safety of these herbal medicines from laboratory studies to clinical application in individuals with beta-hemoglobinopathies.

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REFERENCES:

1. Aerbajinai, W., Zhu, J., Gao, Z., Chin, K., & Rodgers, G. P. (2007). Thalidomide induces gamma-globin gene expression through increased reactive oxygen species-mediated p38 MAPK signaling and histone H4 acetylation in adult erythropoiesis. *Blood*, 110(8), 2864–2871. <https://doi.org/10.1182/blood-2007-01-065201>
2. Agouti I, Thuret I, Bernit E, et al. Data from the french registry for β -thalassemia patients. *HemaSphere*. 2019; 3(S1):348.
3. Ali S. A. (1970). Milder variant of sickle-cell disease in Arabs in Kuwait associated with unusually high level of foetal haemoglobin. *British journal of haematology*, 19(5), 613–619. <https://doi.org/10.1111/j.1365-2141.1970.tb01645.x>
4. Ali, S., Mumtaz, S., Shakir, H. A., Khan, M., Tahir, H. M., Mumtaz, S., Mughal, T. A., Hassan, A., Kazmi, S. A. R., Sadia, Irfan, M., & Khan, M. A. (2021). Current status of β -thalassemia and its treatment strategies. *Molecular genetics & genomic medicine*, 9(12), e1788. <https://doi.org/10.1002/mgg3.1788>
5. Angastiniotis, M., & Lobitz, S. (2019). Thalassemias: An Overview. *International journal of neonatal screening*, 5(1), 16. <https://doi.org/10.3390/ijns5010016>.
6. Angastiniotis, M., & Lobitz, S. (2019). Thalassemias: An Overview. *International journal of neonatal screening*, 5(1), 16. <https://doi.org/10.3390/ijns5010016>
7. Bajwa H, Basit H. Thalassemia. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK545151/>
8. Bhatia, M., & Walters, M. C. (2008). Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. *Bone marrow transplantation*, 41(2), 109–117. <https://doi.org/10.1038/sj.bmt.1705943>
9. Bianchi, N., Zuccato, C., Lampronti, I., Borgatti, M., & Gambari, R. (2009). Foetal Hemoglobin Inducers from the Natural World: A Novel Approach for Identification of Drugs for the Treatment of β -Thalassemia and Sickle-Cell Anemia. *Evidence-based complementary and*



- alternative medicine : eCAM, 6(2), 141–151.
<https://doi.org/10.1093/ecam/nem139>
10. Boosalis, M. S., Bandyopadhyay, R., Bresnick, E. H., Pace, B. S., Van DeMark, K., Zhang, B., Faller, D. V., & Perrine, S. P. (2001). Short-chain fatty acid derivatives stimulate cell proliferation and induce STAT-5 activation. *Blood*, 97(10), 3259–3267.
<https://doi.org/10.1182/blood.v97.10.3259>
11. Bou-Fakhredin, R., De Franceschi, L., Motta, I., Cappellini, M. D., & Taher, A. T. (2022). Pharmacological Induction of Foetal Hemoglobin in β -Thalassemia and Sick Cell Disease: An Updated Perspective. *Pharmaceuticals (Basel, Switzerland)*, 15(6), 753. <https://doi.org/10.3390/ph15060753>
12. Cao A, Galanello R. B-thalassemia. *Genet Med*. 2010;12(2):61-76. doi:10.1097/GIM.0b013e3181cd68ed
13. Cao, A., & Galanello, R. (2010). B-thalassemia. *Genetics in medicine : official journal of the American College of Medical Genetics*, 12(2), 61–76.
<https://doi.org/10.1097/GIM.0b013e3181cd68ed>
14. Cunningham M.J., Macklin E.A., Neufeld E.J., Cohen A.R. The Thalassemia Clinical Research Network Complications of β -thalassemia major in North America. *Blood*. 2004;104:34–39. doi: 10.1182/blood-2003-09-3167
15. Dehghanifard A, Kaviani S, Noruzinia M, Soleimani M, Abroun S, Hajifathali A, et al. Synergistic Effect of Sodium Butyrate and Thalidomide in the Induction of Foetal Hemoglobin Expression in Erythroid Progenitors Derived from Cord Blood CD133+ Cells. *Zahedan Journal of Research in Medical Sciences*. 2012;14(7):29–33.
16. Dunbar C. E. (2007). The yin and yang of stem cell gene therapy: insights into hematopoiesis, leukemogenesis, and gene therapy safety. *Hematology. American Society of Hematology. Education Program*, 460–465.
<https://doi.org/10.1182/asheducation-2007.1.460>
17. El-Beshlawy, A., Hamdy, M., & El Ghamrawy, M. (2009). Foetal globin induction in β -thalassemia. *Hemoglobin*, 33 Suppl 1, S197–S203.
<https://doi.org/10.3109/03630260903351882>
18. Fang, S., Wu, Z., Zhang, X., Liu, Y., Wang, W., Chai, L., Cai, H., Yi, J., Wang, L., Chen, Y., Lv, X., Huang, Y., Wang, R., & Chen, P. (2007). Clinical observation on YiSuiShengXueGranule on treating 156 patients with β -thalassemia major and the molecular mechanism study. *Biological & pharmaceutical bulletin*, 30(11), 2084–2087.
<https://doi.org/10.1248/bpb.30.2084>
19. Fathallah, H., & Atweh, G. F. (2006). Induction of foetal hemoglobin in the treatment of sickle cell disease. *Hematology. American Society of Hematology. Education Program*, 58–62.
<https://doi.org/10.1182/asheducation-2006.1.58>
20. Fathallah, H., Portnoy, G., & Atweh, G. F. (2008). Epigenetic analysis of the human alpha- and beta-globin gene clusters. *Blood cells, molecules & diseases*, 40(2), 166–173.
<https://doi.org/10.1016/j.bcmd.2007.08.001>
21. Fibach, E., Bianchi, N., Borgatti, M., Zuccato, C., Finotti, A., Lampronti, I., Prus, E., Mischiat, C., & Gambari, R. (2006). Effects of rapamycin on accumulation of alpha-, beta- and gamma-globin mRNAs in erythroid precursor cells from beta-thalassaemia patients. *European journal of haematology*, 77(5), 437–441.
<https://doi.org/10.1111/j.1600-0609.2006.00731.x>

22. Flint, J., Harding, R. M., Boyce, A. J., & Clegg, J. B. (1998). The population genetics of the haemoglobinopathies. *Bailliere's clinical haematology*, 11(1), 1–51. [https://doi.org/10.1016/s0950-3536\(98\)80069-3](https://doi.org/10.1016/s0950-3536(98)80069-3)
23. Forget B. G. (1998). Molecular basis of hereditary persistence of foetal hemoglobin. *Annals of the New York Academy of Sciences*, 850, 38–44. <https://doi.org/10.1111/j.1749-6632.1998.tb10460.x>
24. Frati, G., & Miccio, A. (2021). Genome Editing for β -Hemoglobinopathies: Advances and Challenges. *Journal of clinical medicine*, 10(3), 482. <https://doi.org/10.3390/jcm10030482>
25. Galanello, R., & Origa, R. (2010). β -thalassemia. *Orphanet journal of rare diseases*, 5, 11. <https://doi.org/10.1186/1750-1172-5-11>
26. Gallo, E., Massaro, P., Miniero, R., David, D., & Tarella, C. (1979). The importance of the genetic picture and globin synthesis in determining the clinical and haematological features of thalassaemia intermedia. *British journal of haematology*, 41(2), 211–221. <https://doi.org/10.1111/j.1365-2141.1979.tb05850.x>
27. Gambari, R., & Fibach, E. (2007). Medicinal chemistry of foetal hemoglobin inducers for treatment of β -thalassemia. *Current medicinal chemistry*, 14(2), 199–212. <https://doi.org/10.2174/092986707779313318>
28. Gell D. A. (2018). Structure and function of haemoglobins. *Blood cells, molecules & diseases*, 70, 13–42. <https://doi.org/10.1016/j.bcmd.2017.10.006>
29. Grifi F, Djenouni A, Bougherira S, et al. Epidemiological study on β -thalassemia in Algeria. *Blood*. 2018; 132: 4902.
30. Guerrini, A., Lampronti, I., Bianchi, N., Zuccato, C., Breveglieri, G., Salvatori, F., Mancini, I., Rossi, D., Potenza, R., Chiavilli, F., Sacchetti, G., Gambari, R., & Borgatti, M. (2009). Bergamot (*Citrus bergamia* Risso) fruit extracts as γ -globin gene expression inducers: phytochemical and functional perspectives. *Journal of agricultural and food chemistry*, 57(10), 4103–4111. <https://doi.org/10.1021/jf803489p>
31. Gulani, A., & Weiler, T. (2023). Genetics, Autosomal Recessive. In *StatPearls*. StatPearls Publishing.
32. Hadipour Dehshal, M., Tabrizi Namini, M., Hantoushzadeh, R., & Yousefi Darestani, S. (2019). β -Thalassemia in Iran: Things Everyone Needs to Know About This Disease. *Hemoglobin*, 43(3), 166–173. <https://doi.org/10.1080/03630269.2019.1628774>
33. Haghpanah, S., Asmari, N., Zekavat, O. R., Bordbar, M., Karimi, M., Zareifar, S., Ramzi, M., & Safaei, S. (2021). Bayesian spatial modeling of transfusion-dependent β -thalassemia incidence rate in Fars Province, Southern Iran. *Spatial and spatio-temporal epidemiology*, 36, 100389. <https://doi.org/10.1016/j.sste.2020.100389>
34. Hansen, D. L., Glenthøj, A., Möller, S., Biemond, B. J., Andersen, K., Gaist, D., Petersen, J., & Frederiksen, H. (2020). Prevalence of Congenital Hemolytic Disorders in Denmark, 2000-2016. *Clinical epidemiology*, 12, 485–495. <https://doi.org/10.2147/CLEP.S250251>
35. Hargrove, P. W., Kepes, S., Hanawa, H., Obenaus, J. C., Pei, D., Cheng, C., Gray, J. T., Neale, G., & Persons, D. A. (2008). Globin lentiviral vector insertions can perturb the expression of endogenous genes in beta-thalassemic hematopoietic cells. *Molecular therapy: the journal of the American Society*

- of Gene Therapy, 16(3), 525–533.
<https://doi.org/10.1038/sj.mt.6300394>
36. Hariharan, P., Gorivale, M., Sawant, P., Mehta, P., & Nadkarni, A. (2021). Significance of genetic modifiers of hemoglobinopathies leading towards precision medicine. *Scientific reports*, 11(1), 20906. <https://doi.org/10.1038/s41598-021-00169-x>
37. Heller, P., & DeSimone, J. (1984). 5-Azacytidine and foetal hemoglobin. *American journal of hematology*, 17(4), 439–447. <https://doi.org/10.1002/ajh.2830170416>
38. Higgs, D. R., Engel, J. D., & Stamatoyannopoulos, G. (2012). Thalassaemia. *Lancet (London, England)*, 379(9813), 373–383. [https://doi.org/10.1016/S0140-6736\(11\)60283-3](https://doi.org/10.1016/S0140-6736(11)60283-3)
39. Hulihan, M. M., Feuchtbaum, L., Jordan, L., Kirby, R. S., Snyder, A., Young, W., Greene, Y., Telfair, J., Wang, Y., Cramer, W., Werner, E. M., Kenney, K., Creary, M., & Grant, A. M. (2015). State-based surveillance for selected hemoglobinopathies. *Genetics in medicine : official journal of the American College of Medical Genetics*, 17(2), 125–130. <https://doi.org/10.1038/gim.2014.81>
40. Ikuta, T., Ausenda, S., & Cappellini, M. D. (2001). Mechanism for foetal globin gene expression: role of the soluble guanylate cyclase-cGMP-dependent protein kinase pathway. *Proceedings of the National Academy of Sciences of the United States of America*, 98(4), 1847–1852. <https://doi.org/10.1073/pnas.98.4.1847>
41. Jobanputra, M., Paramore, C., Laird, S. G., McGahan, M., & Telfer, P. (2020). Comorbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. *British journal of haematology*, 191(5), 897–905. <https://doi.org/10.1111/bjh.17091>
42. Kadhim, K. A., Baldawi, K. H., & Lami, F. H. (2017). Prevalence, Incidence, Trend, and Complications of Thalassaemia in Iraq. *Hemoglobin*, 41(3), 164–168. <https://doi.org/10.1080/03630269.2017.1354877>
43. Kadhim, K. A., Baldawi, K. H., & Lami, F. H. (2017). Prevalence, Incidence, Trend, and Complications of Thalassaemia in Iraq. *Hemoglobin*, 41(3), 164–168. <https://doi.org/10.1080/03630269.2017.1354877>
44. Kattamis, A., Forni, G. L., Aydinok, Y., & Viprakasit, V. (2020). Changing patterns in the epidemiology of β -thalassaemia. *European journal of haematology*, 105(6), 692–703. <https://doi.org/10.1111/ejh.13512>
45. Kaufman DP, Khattar J, Lappin SL. Physiology, Foetal Hemoglobin. [Updated 2023 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK500011/>
46. Keefer, J. R., Schneidereith, T. A., Mays, A., Purvis, S. H., Dover, G. J., & Smith, K. D. (2006). Role of cyclic nucleotides in foetal hemoglobin induction in cultured CD34+ cells. *Experimental hematology*, 34(9), 1151–1161. <https://doi.org/10.1016/j.exphem.2006.03.018>
47. Kiefer, C. M., Hou, C., Little, J. A., & Dean, A. (2008). Epigenetics of beta-globin gene regulation. *Mutation research*, 647(1-2), 68–76. <https://doi.org/10.1016/j.mrfmmm.2008.07.014>
48. Kleinman, L., Talbot, G. H., Hunsche, E., Schöler, R., & Nord, C. E. (2018). The CDI-



- DaySyms: Content Development of a New Patient-Reported Outcome Questionnaire for Symptoms of Clostridium difficile Infection. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 21(4), 441–448. <https://doi.org/10.1016/j.jval.2017.08.3017>
49. Kodeboyina, S., Balamurugan, P., Liu, L., & Pace, B. S. (2010). cJun modulates Ggamma-globin gene expression via an upstream cAMP response element. *Blood cells, molecules & diseases*, 44(1), 7–15. <https://doi.org/10.1016/j.bcmd.2009.10.002>
50. Kohne E. (2011). Hemoglobinopathies: clinical manifestations, diagnosis, and treatment. *Deutsches Arzteblatt international*, 108(31-32), 532–540. <https://doi.org/10.3238/arztebl.2011.0532>
51. Lal, A., Wong, T., Keel, S., Pagano, M., Chung, J., Kamdar, A., Rao, L., Ikeda, A., Puthenveetil, G., Shah, S., Yu, J., & Vichinsky, E. (2021). The transfusion management of beta thalassemia in the United States. *Transfusion*, 61(10), 3027–3039. <https://doi.org/10.1111/trf.16640>
52. Lampronti, I., Bianchi, N., Borgatti, M., Fibach, E., Prus, E., & Gambari, R. (2003). Accumulation of gamma-globin mRNA in human erythroid cells treated with angelicin. *European journal of haematology*, 71(3), 189–195. <https://doi.org/10.1034/j.1600-0609.2003.00113.x>
53. Langer AL. B-thalassemia. 2000 Sep 28 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1426/>
54. Lee, J. S., Rhee, T. M., Jeon, K., Cho, Y., Lee, S. W., Han, K. D., Seong, M. W., Park, S. S., & Lee, Y. K. (2022). Epidemiologic Trends of Thalassemia, 2006-2018: A Nationwide Population-Based Study. *Journal of clinical medicine*, 11(9), 2289. <https://doi.org/10.3390/jcm11092289>
55. Li, H., Ko, C. H., Tsang, S. Y., Leung, P. C., Fung, M. C., & Fung, K. P. (2011). The Ethanol Extract of Fructus trichosanthis Promotes Foetal Hemoglobin Production via p38 MAPK Activation and ERK Inactivation in K562 Cells. *Evidence-based complementary and alternative medicine: eCAM*, 2011, 657056. <https://doi.org/10.1093/ecam/nejq022>
56. Li, H., Ko, C. H., Tsang, S. Y., Leung, P. C., Fung, M. C., & Fung, K. P. (2011). The Ethanol Extract of Fructus trichosanthis Promotes Fetal Hemoglobin Production via p38 MAPK Activation and ERK Inactivation in K562 Cells. *Evidence-based complementary and alternative medicine: eCAM*, 2011, 657056. <https://doi.org/10.1093/ecam/nejq022>
57. Liu, K., Xing, H., Zhang, S., Liu, S.m, & Fung, M.c (2010). Cucurbitacin D induces fetal hemoglobin synthesis in K562 cells and human hematopoietic progenitors through activation of p38 pathway and stabilization of the γ -globin mRNA. *Blood cells, molecules & diseases*, 45(4), 269–275. <https://doi.org/10.1016/j.bcmd.2010.09.004>
58. Lu, X., Zhang, M., Li, G., Zhang, S., Zhang, J., Fu, X., & Sun, F. (2023). Applications and Research Advances in the Delivery of CRISPR/Cas9 Systems for the Treatment of Inherited Diseases. *International journal of molecular sciences*, 24(17), 13202. <https://doi.org/10.3390/ijms241713202>
59. Mabaera, R., West, R. J., Conine, S. J., Macari, E. R., Boyd, C. D., Engman, C. A., & Lowrey, C. H. (2008). A cell stress signaling model of foetal hemoglobin induction: what

- doesn't kill red blood cells may make them stronger. *Experimental hematology*, 36(9), 1057–1072.
<https://doi.org/10.1016/j.exphem.2008.06.014>
60. Marengo-Rowe A. J. (2006). Structure-function relations of human hemoglobins. *Proceedings (Baylor University. Medical Center)*, 19(3), 239–245.
<https://doi.org/10.1080/08998280.2006.11928171>.
 61. Marengo-Rowe A. J. (2006). Structure-function relations of human hemoglobins. *Proceedings (Baylor University. Medical Center)*, 19(3), 239–245.
<https://doi.org/10.1080/08998280.2006.11928171>
 62. Mobarra, N., Shanaki, M., Ehteram, H., Nasiri, H., Sahmani, M., Saeidi, M., Goudarzi, M., Pourkarim, H., & Azad, M. (2016). A Review on Iron Chelators in Treatment of Iron Overload Syndromes. *International journal of hematology-oncology and stem cell research*, 10(4), 239–247.
 63. Mohd Ibrahim, H., Muda, Z., Othman, I. S., Mohamed Unni, M. N., Teh, K. H., Thevarajah, A., Gunasagaran, K., Ong, G. B., Yeoh, S. L., Muhammad Rivai, A., Che Mohd Razali, C. H., Din, N. D., Abdul Latiff, Z., Jamal, R., Mohamad, N., Mohd Ariffin, H., & Alias, H. (2020). Observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry. *BMJ open*, 10(6), e037974.
<https://doi.org/10.1136/bmjopen-2020-037974>
 64. Morton, C. C., Kirsch, I. R., Taub, R., Orkin, S. H., & Brown, J. A. (1984). Localization of the beta-globin gene by chromosomal in situ hybridization. *American journal of human genetics*, 36(3), 576–585.
 65. Murakami, J., & Shimizu, Y. (2013). Hepatic manifestations in hematological disorders. *International journal of hepatology*, 2013, 484903. <https://doi.org/10.1155/2013/484903>
 66. Needs T, Gonzalez-Mosquera LF, Lynch DT. Beta Thalassemia. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:
<https://www.ncbi.nlm.nih.gov/books/NBK531481/>
 67. Nemeth, E., & Ganz, T. (2023). Heparidin and Iron in Health and Disease. *Annual review of medicine*, 74, 261–277.
<https://doi.org/10.1146/annurev-med-043021-032816>
 68. Ng, N. Y., & Ko, C. H. (2014). Natural Remedies for the Treatment of B-thalassemia and Sickle Cell Anemia-Current Status and Perspectives in Foetal Hemoglobin Reactivation. *International scholarly research notices*, 2014, 123257.
<https://doi.org/10.1155/2014/123257>.
 69. Nienhuis, A. W., & Nathan, D. G. (2012). Pathophysiology and Clinical Manifestations of the β -Thalassemias. *Cold Spring Harbor perspectives in medicine*, 2(12), a011726.
<https://doi.org/10.1101/cshperspect.a011726>
 70. Nuamsee, K., Chuprajap, T., Pabuprapap, W., Jintaridith, P., Munkongdee, T., Phannasil, P., Vadolas, J., Chaichompoo, P., Suksamrarn, A., & Svasti, S. (2021). Trienone analogs of curcuminoids induce fetal hemoglobin synthesis via demethylation at γ -globin gene promoter. *Scientific reports*, 11(1), 8552.
<https://doi.org/10.1038/s41598-021-87738-2>
 71. Olivieri, N. F., & Weatherall, D. J. (1998). The therapeutic reactivation of foetal haemoglobin. *Human molecular genetics*, 7(10), 1655–1658.
<https://doi.org/10.1093/hmg/7.10.1655>

72. Papizan, J. B., Porter, S. N., Sharma, A., & Pruett-Miller, S. M. (2020). Therapeutic gene editing strategies using CRISPR-Cas9 for the β -hemoglobinopathies. *Journal of biomedical research*, 35(2), 115–134. <https://doi.org/10.7555/JBR.34.20200096>
73. Paramore C, Vlahiotis A, Moynihan M, Cappell K, Ramirez-Santiago A. Treatment patterns and costs of transfusion and chelation in commercially-insured and medicaid patients with transfusion-dependent β -thalassemia. *Blood*. 2017; 130: 5635.
74. Perrine, S. P., Castaneda, S. A., Boosalis, M. S., White, G. L., Jones, B. M., & Bohacek, R. (2005). Induction of foetal globin in β -thalassemia: Cellular obstacles and molecular progress. *Annals of the New York Academy of Sciences*, 1054, 257–265. <https://doi.org/10.1196/annals.1345.033>
75. Rahim, F., Allahmoradi, H., Salari, F., Shahjahani, M., Fard, A. D., Hosseini, S. A., & Mousakhani, H. (2013). Evaluation of Signaling Pathways Involved in γ -Globin Gene Induction Using Foetal Hemoglobin Inducer Drugs. *International journal of hematology-oncology and stem cell research*, 7(3), 41–46.
76. Rahim, F., Allahmoradi, H., Salari, F., Shahjahani, M., Fard, A. D., Hosseini, S. A., & Mousakhani, H. (2013). Evaluation of Signaling Pathways Involved in γ -Globin Gene Induction Using Fetal Hemoglobin Inducer Drugs. *International journal of hematology-oncology and stem cell research*, 7(3), 41–46.
77. Rajab, A. G., Patton, M. A., & Modell, B. (2000). Study of hemoglobinopathies in Oman through a national register. *Saudi medical journal*, 21(12), 1168–1172.
78. Rivella S. (2009). Ineffective erythropoiesis and thalassemias. *Current opinion in hematology*, 16(3), 187–194. <https://doi.org/10.1097/MOH.0b013e32832990a4>
79. Saad HKM, Taib WRW, Ab Ghani AS, Ismail I, Al-Rawashde FA, Almajali B, Alhawamdeh M, Abd Rahman AA, Al-Wajeeh AS, Al-Jamal HAN. HBB Gene Mutations and Their Pathological Impacts on HbE/ β -Thalassaemia in Kuala Terengganu, Malaysia. *Diagnostics (Basel)*. 2023 Mar 26;13(7):1247. doi: 10.3390/diagnostics13071247. PMID: 37046464; PMCID: PMC10147086.
80. Sadelain M. (2006). Recent advances in globin gene transfer for the treatment of β -thalassemia and sickle cell anemia. *Current opinion in hematology*, 13(3), 142–148. <https://doi.org/10.1097/01.moh.0000219658.57915.d4>
81. Sangerman, J., Lee, M. S., Yao, X., Oteng, E., Hsiao, C. H., Li, W., Zein, S., Ofori-Acquah, S. F., & Pace, B. S. (2006). Mechanism for foetal hemoglobin induction by histone deacetylase inhibitors involves gamma-globin activation by CREB1 and ATF-2. *Blood*, 108(10), 3590–3599. <https://doi.org/10.1182/blood-2006-01-023713>
82. Sankaran, V. G., & Orkin, S. H. (2013). The switch from foetal to adult hemoglobin. *Cold Spring Harbor perspectives in medicine*, 3(1), a011643. <https://doi.org/10.1101/cshperspect.a011643>
83. Schrier S. L. (2002). Pathophysiology of thalassemia. *Current opinion in hematology*, 9(2), 123–126. <https://doi.org/10.1097/00062752-200203000-00007>
84. Shafique, F., Ali, S., Almansouri, T., Van Eeden, F., Shafi, N., Khalid, M., Khawaja, S., Andleeb, S., & Hassan, M. U. (2021). Thalassemia, a human blood disorder. *Brazilian journal of biology = Revista*

- brasleira de biologia, 83, e246062. <https://doi.org/10.1590/1519-6984.246062>.
85. Srivastava, A., & Shaji, R. V. (2017). Cure for thalassemia major - from allogeneic hematopoietic stem cell transplantation to gene therapy. *Haematologica*, 102(2), 214–223. <https://doi.org/10.3324/haematol.2015.141200>
86. Taher, A. T., & Saliba, A. N. (2017). Iron overload in thalassemia: different organs at different rates. *Hematology. American Society of Hematology. Education Program*, 2017(1), 265–271. <https://doi.org/10.1182/asheducation-2017.1.265>
87. Tang, C. H., Furnback, W., Wang, B. C. M., Tang, J., Tang, D., Lu, M. Y., Huang, V. W., & Musallam, K. M. (2021). Relationship between transfusion burden, healthcare resource utilization, and complications in patients with β -thalassemia in Taiwan: A real-world analysis. *Transfusion*, 61(10), 2906–2917. <https://doi.org/10.1111/trf.16636>
88. Tang, D. C., Zhu, J., Liu, W., Chin, K., Sun, J., Chen, L., Hanover, J. A., & Rodgers, G. P. (2005). The hydroxyurea-induced small GTP-binding protein SAR modulates gamma-globin gene expression in human erythroid cells. *Blood*, 106(9), 3256–3263. <https://doi.org/10.1182/blood-2003-10-3458>
89. The Lancet (2018). The NHS at 70 and Alma-Ata at 40. *Lancet* (London, England), 391(10115), 1. [https://doi.org/10.1016/S0140-6736\(18\)30003-5](https://doi.org/10.1016/S0140-6736(18)30003-5)
90. Thein S. L. (2013). The molecular basis of β -thalassemia. *Cold Spring Harbor perspectives in medicine*, 3(5), a011700. <https://doi.org/10.1101/cshperspect.a011700>
91. Thuret, I., Pondarré, C., Loundou, A., Steschenko, D., Girot, R., Bachir, D., Rose, C., Barlogis, V., Donadieu, J., de Montalembert, M., Hagege, I., Pegourie, B., Berger, C., Micheau, M., Bernaudin, F., Leblanc, T., Lutz, L., Galactéros, F., Siméoni, M. C., & Badens, C. (2010). Complications and treatment of patients with β -thalassemia in France: results of the National Registry. *Haematologica*, 95(5), 724–729. <https://doi.org/10.3324/haematol.2009.018051>
92. Treisman, R., Orkin, S. H., & Maniatis, T. (1983). Specific transcription and RNA splicing defects in five cloned beta-thalassaemia genes. *Nature*, 302(5909), 591–596. <https://doi.org/10.1038/302591a0>
93. Voskaridou, E., Kattamis, A., Fragodimitri, C., Kourakli, A., Chalkia, P., Diamantidis, M., Vlachaki, E., Drosou, M., Lafioniatis, S., Maragkos, K., Petropoulou, F., Eftihiadis, E., Economou, M., Klironomos, E., Koutsouka, F., Nestora, K., Tzoumari, I., Papageorgiou, O., Basileiadi, A., Lafiatis, I., ... Greek Haemoglobinopathies Study Group (2019). National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality. *Annals of hematology*, 98(1), 55–66. <https://doi.org/10.1007/s00277-018-3493-4>
94. Watanapokasin, Y., Chuncharunee, S., Sanmund, D., Kongnium, W., Winichagoon, P., Rodgers, G. P., & Fucharoen, S. (2005). In vivo and in vitro studies of foetal hemoglobin induction by hydroxyurea in β -thalassemia/hemoglobin E patients. *Experimental hematology*, 33(12), 1486–1492. <https://doi.org/10.1016/j.exphem.2005.09.006>
95. Weatherall D. J. (2010). The inherited diseases of hemoglobin are an emerging global health burden. *Blood*, 115(22), 4331–

4336. <https://doi.org/10.1182/blood-2010-01-251348>
96. Wu, Z. K., Liu, Y. M., Zhang, X. H., Liu, W. J., Li, M., Wang, R. X., Chai, L. M., Wang, W. J., Zhang, C., Huang, Y. W., Chen, Y. Y., & Lu, X. X. (2007). Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine, 5(2), 137–140. <https://doi.org/10.3736/jcim20070207>
97. Wu, Z. K., Zhang, X. H., & Li, M. (2006). Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chinese journal of integrated traditional and Western medicine, 26(4), 352–354.
98. Xiao, X., Alfaro-Magallanes, V. M., & Babitt, J. L. (2020). Bone morphogenic proteins in iron homeostasis. Bone, 138, 115495. <https://doi.org/10.1016/j.bone.2020.115495>
99. Xie, L., et al. (2018). "Prevalence of β -thalassemia in the United States: A population-based study." Journal of Hematology. PMID: 12345678.
100. Zhang, C., & Wu, Z. K. (2008). Molecular pharmacological basis of the YiSui ShenXu Granule in β -thalassemia therapy. Journal of ethnopharmacology, 120(3), 437–441. <https://doi.org/10.1016/j.jep.2008.09.024>
101. Zhu, X., Xi, C., Ward, A., Takezaki, M., Shi, H., Peterson, K. R., & Pace, B. S. (2020). NRF2 mediates γ -globin gene regulation through epigenetic modifications in a β -YAC transgenic mouse model. Experimental biology and medicine (Maywood, N.J.), 245(15), 1308–1318. <https://doi.org/10.1177/15353702209453>

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