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Review Article

Therapeutic role of natural agents in beta-thalassemia: A review

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ABSTRACT

Beta-thalassemia is a genetic disease caused by either reduced production or complete absence of beta-globin chains. It is characterized by dyserythropoiesis which leads to the development of early erythroid precursor cells into immature erythroblasts. Patients with high level of fetal hemoglobin (HbF) develop less severe symptoms and survive normally. Therefore, augmentation of the level of HbF has been an effective therapeutic approach for patients of beta-thalassemia. Iron overload is the leading cause of mortality in beta-thalassemia. Natural pharmacological agents have been used to stimulate the HbF level and reduce iron overload in patients suffering from this deleterious disease. This is an efficient way to treat beta-thalassemia as it also provides better correlation between *in vivo* and *in vitro* synthesis of beta-globin chains in patients. Being economic, it is also affordable for the patients in developing countries. This article reports some natural compounds of plant origin having a therapeutic role in inducing HbF level and possessing chelation therapy in beta-thalassemia patients.

1. Introduction

Beta-thalassemia is one of the most frequent hereditary diseases in the world.[1] Beta-thalassemia syndromes describe a group of genetic blood disorders caused by decreased or absent synthesis of the beta-globin chain, resulting in reduced amount of hemoglobin in red blood cells (RBC), low RBC production and anemia.[2] The intensiveness of beta-thalassemia is associated with the extent of alpha and non alpha globin chains imbalance.[3] It has three main forms: beta-thalassemia minor, beta-thalassemia intermediate and beta-thalassemia major. Beta-thalassemia minor patients have no symptoms and the patient may lead a normal life. Patients with beta-thalassemia intermediate (TI) have moderate anemia whereas beta-thalassemia major patients have severe anemia and also require frequent blood transfusion.[2] Iron overload is a frequent complexity found in thalassemic patients which eventually lead to the organ impairment and rise in mortality rates. Iron overload develops due to two main mechanisms: increased iron absorption due to inefficient erythropoiesis and blood transfusions.[4]

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1.1. *Natural strategies for the treatment of beta-thalassemia*

Recently, much stress has been focused on natural strategies for the treatment of beta-thalassemia. Natural inducers can increase fetal hemoglobin level and can also reduce iron overload in beta-thalassemic patients (Fig. 1).[2,5]

2. Natural inducers for fetal hemoglobin production

High level of fetal hemoglobin can improve the severity of beta-thalassemia. The formation of defective beta-globin molecule in beta-thalassemic patients can be stabilized by the production of gamma globin (beta-like globin molecule), which combines with alpha-globin chains to form fetal hemoglobin. The increase in the production of gamma globin lowers the alpha/beta-chain imbalance resulting in the improvement of decreased hemolysis, ineffective erythropoiesis and increased total hemoglobin level.[6] Natural inducers used to augment fetal hemoglobin production in beta-thalassemic patients (Fig. 2) are discussed below:

2.1. *Angelicin*

Angelicin (contained in plant extracts of *Angelica archangelica* and *Aegle marmelos*) is a mono-functional isopsoralen that possess anti-proliferative activity and is able to bind DNA without producing cross linking between inter-strand bands. Angelicin and its analog bergapten have been used to treat different skin diseases. They have also been used in antimycotic therapy. It has been experimentally found that the extract of *Angelica archangelica* is a potent inducer erythroid cell as it increases fetal hemoglobin level in erythroid progenitors taken from normal patients. It also increases the level of γ globin mRNA in erythroid precursors of beta-thalassemic patients.[7,8] The activity of angelicin has been checked by using two experimental cell systems, the human leukemic K562 cell line and human erythroid progenitors from normal donors. It has been observed that angelicin is a potent inducer of erythroid differentiation, gamma globin gene expression and fetal hemoglobin (HbF) production, thereby making it useful in the treatment of beta-thalassemia.[7]

2.2. *Rapamycin*

Rapamycin is a macrocyclic fermented product produced by *Streptomyces hygroscopicus*. Initially, its role as an antitumor and antifungal agent was tested. As it possesses lymphopenic properties therefore it is known to be a useful immunosuppressant.[9] It is FDA (food and drug administration) approved agent used for the prevention of acute renal allograft rejection. Its activity was tested by using two cell systems, the human leukemia K562 cell line and human erythroid progenitors isolated from normal donors and beta-thalassemia patients. When K562 cells were cultured in the presence of rapamycin, it induced activation and differentiation of K562 cells. Differentiation of K562 cells is associated with an increased expression of γ globin mRNA. It has been observed that rapamycin is more efficient than hydroxyurea for stimulating the production of γ globin mRNA and increasing HbF level. Rapamycin was found to increase HbF level in beta-thalassemic patients.[10]

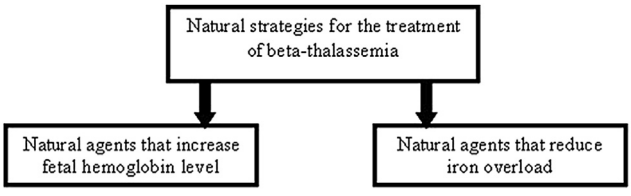

Fig. 1 – Natural strategies for the treatment of beta-thalassemia.

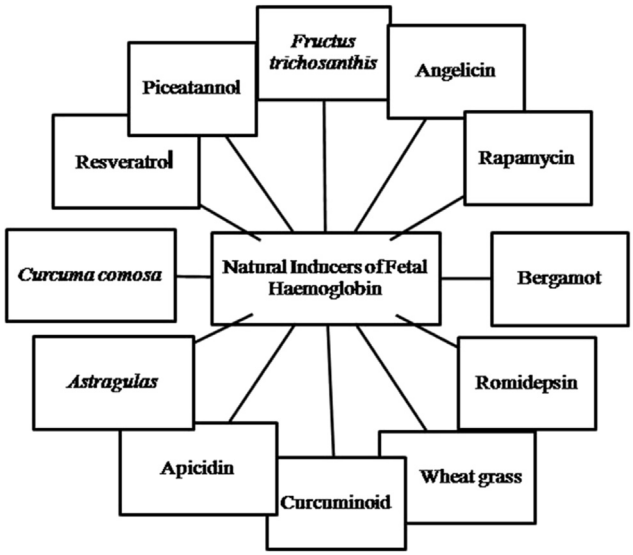

Fig. 2 – Natural inducers of fetal hemoglobin.

2.3. *Fructus trichosanthis (FT)*

FT (fruit of *Trichosanthes kirilowii* MAXIM) is one of the most commonly used Chinese herbs. According to the Chinese medicine theory, FT is useful in treating breast cancer, diabetes, leukemia and bronchial diseases. It has been reported that the ethanol extract of FT significantly increased γ-globin mRNA expression and HbF level in K562 cultured cells. Its inducing effect is due to up-regulation of p38 MAPK (mitogen activated protein kinase) signaling pathway and down-regulation of ERK (extracellular regulated protein kinase) signaling pathway. An ethanolic extract of the FT increases the HbF level to 2.6 folds in beta-thalassemia cells. Its inducing effect has been found to be more as compared to hydroxyurea positive control cells. The component of FT extract responsible for inducing HbF level in cultured cells is still unknown. There is a need to find out the component responsible for HbF induction by checking the activity of all the components present in raw FT. In order to promote the usage of FT ethanol (FT-EtOH) extract for the treatment of thalassemia, there is a need to elucidate the effect of FT-EtOH on precursor cells