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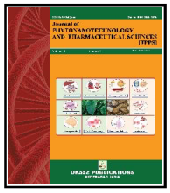

Review Article : Open Access

A comprehensive review of Indian medicinal plants used in the treatment and management of thalassemia and related disorders

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Abstract

Thalassemia, an inherited hemoglobin disorder of red blood cells, leading to ineffective erythropoiesis and associated iron overload, is a major cause of morbidity. Currently, limited conventional treatments, such as blood transfusions and iron chelation, have their downsides (high cost and adverse events). In recent research, plants have been shown to tackle thalassemia, as phytochemistry-based interventions have been identified through Indian medicinal plants to control this hematologic compromise in India. In this review, we discuss the therapeutic potential of several medicinal plants (*Phyllanthus emblica*, *Terminalia chebula*, *Curcuma longa*, and *Withania somnifera*) with antioxidant/anti-inflammatory/ferrous chelating and HbF-inducing properties. Oxidative stress management, alleviation of iron toxicity and induction of normal hemoglobin is performed by flavonoids, alkaloids, tannins and polyphenols containing these bioactive compounds. Studies in both preclinical humans and humans suggest that these herbs can regulate hemoglobin synthesis, increase red blood cell survival and ameliorate associated morbidity from anemia. These remedies stand against several challenges, such as standardisation, quality control, safety validation and regulatory acceptance, which hinder their non-controversial use in clinical practice. The future of herbal thalassemia management is not in pharmacological validation but in advanced molecular studies and integrative approaches, including traditional methods, with modern biomedicine. The urgent need for additional studies to develop plant-based therapeutic agents for thalassemia as adjunct or alternative treatments will be highlighted in this review. Indian medicinal plants can transform thalassemia management through a bridge between traditional knowledge and scientific validation.

1. Introduction

Thalassemia comprises a group of genetic blood disorders distinguished by decreased hypochromic microcytic abnormal hemoglobin1. The word thalassemia is derived from the Greek word thalassaemia, meaning “sea”, and new Latin anemia, from the Greek word hema, meaning “blood”. The name “Mediterranean anemia” was first described by people of Mediterranean ethnicities. Later, as the genetics of the condition became elucidated, the name “Mediterranean anemia” morphed into thalassemia major. The term thalassemia was first used in 1932. Symptoms depend on the type and can be absent or severe. An individual usually has low red blood cells to varying degrees, ranging from mild to severe anemia. Symptoms of anemia include tiredness and pale skin. There could be bone changes, an enlarged spleen, yellowish skin, and dark urine, and in children, there might be slow growth. Thalassemia symptoms can cause confusion and discomfort in daily life. Specifically, this disorder is often characterized by the late onset of anemia in children and adolescents. Thalassemias are inherited genetic disorders transmitted through parental lineages. The classification of thalassemia disorders includes two primary categories: alpha thalassemia and beta thalassemia. The intensity of alpha and beta thalassemia conditions is related directly to the number of missing alpha globin genes out of four possible or beta globin genes out of two possible genes. The typical diagnostic process involves blood tests such as complete blood count alongside specialized hemoglobin tests and genetic tests. Through prenatal testing methods, doctors can identify conditions before a child is born (Rahamat Unissa *et al.,* 2018). The determination of treatment methods varies according to both type and severity factors. Individuals with advanced-stage disease frequently undergo regular blood transfusions alongside iron chelation therapy and folic acid supplementation. The administration of deferoxamine or deferasirox enables iron chelation. There are rare instances where medical professionals might consider bone marrow transplantation as a treatment option. Transformations can lead to iron overload, which then causes heart or liver disease, while patients also face risks of infections and developing osteoporosis. An excessively enlarged spleen might necessitate surgical removal. Mutations in genes encoding alpha- or beta-chains of hemoglobin due to defects in DNA lead to proper hemoglobin protein, *i.e.,* the erythrocyte oxygen carrier (hemoglobin) is not synthesized at the molecular level (Tilva *et al.,* 2022).

Characteristically (pathophysiology) thalassemia is associated with globin chain synthesis homeostasis defects that lead to relative over/ underproduction of either alpha or beta globin chains, which eventually manifests as disturbances in erythrocyte production and function. Thalassemia is a diverse group of inherited hematological disorders characterized by decreased synthesis of hemoglobin chains, causing hypochromic, microcytic anemia due to variable thromcobra

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resistance. Thus, homozygous thalassemia (*e.g.*, beta thalassemia) represents an excess of aloha chains that results in cytoplasmic erythrocyte inclusions and anemia, bone hyperplasia, osteoporosis and sequelae, such as hemosiderosis. This involves the accumulation of mismatched globin chains and later leads to ineffective hemolytic erythropoiesis *via* mechanisms related to accelerated apoptosis resulting from excess alpha-globin in an erythroid precursor; abnormalities in the beta-globin chain synthesized in β thalassemia result in maturation defects in the erythroid lineage, premature red cell clearance and mixed-chromatic cells in peripheral blood, with iron overload as the main cause of death caused by tissue damage. A reduction in globulin chain synthesis abnormally induces premature cell death, ineffective erythropoiesis and mild to moderate hemolytic anemia (Sadiq *et al.,* 2024).

2. Traditional Indian medicine and herbal approaches

India has a vast and long history of traditional medicine, such as Ayurveda, Siddha and Unani, which are important systems for healthcare in India. Traditional healing systems are holistic and rely on herbal remedies to reestablish balance. Many herbs are used for diseases, ranging widely from common folk symptoms to large categories, such as hematological disorders, such as thalassemia, which are non-functioning. Indian medicinal plants have considerable therapeutic potential, and several herbs are known to possess hematopoietic, antioxidant and iron-chelating properties that can be used in the management of thalassemia and associated issues (Pandey *et al.,* 2013).

2.1 Ayurvedic approach to thalassemia

Ayurveda classified blood disorders as "Pandu Roga" (anemia) or "Raktapitta" (bleeding disorder) along with herbal interventions for remeddling with blood, increasing the oxygen-carrying capacity and iron metabolism. Hematopoietic herbs, *Phyllanthus emblica* (Amla), *Terminalia chebula* (Haritaki) and *Tinospora cordifolia* (Guduchi), are composed of germinal bioflavonoid contents, and hemostimulators increase the production of hemoglobin, protect against oxidative stress and immunomodulatory. In the past, Ayurvedic formulations such as punarnavadi gurni and drakshasava were used for treating anemias and certain other blood-related problems (Samal, 2016).

Table 1: Herbal remedies for thalassemia management and blood health (Tilva *et al.,* 2022)

Herbal remedy	Benefits
Kumara-Kalyana rasa	Helps in RBC formation, boosts energy, reduces weakness, enhances immunity, and prevents recurrent infections.
Pravala pisti	Aids in anemia treatment promote protein formation for healthy RBCs, strengthen immunity, and increase energy.
Kaharava pisti	Supports healthy RBC formation, reduces weakness, and improves blood circulation.
Moti pisti	Helps in RBC and hemoglobin formation, reduces thalassemia risk, and prevents disease complications.
Giloy sattva	Traditionally used for blood disorders, supports RBC production, increases blood supply, and enhances organ function.
Pravala pancamrta	Supports thalassemia management, promotes healthy body function, aids RBC and protein formation.

2.2 Siddha and unani contributions

The Siddha and Unani systems of medicine also depend on the use of herbs for blood cleansing and revitalization. Some of the commonly used rejuvenating and adaptogenic herbs for maintaining the integrity of red blood cells and reducing oxidative damage are *Withania somnifera* (Ashwagandha) and *Hibiscus rosa-sinensis* (Jaswand) (Husain *et al.,* 2023).

Table 2: Indian medicinal plants and Unani remedies for thalassemia management (Husain *et al.,* 2023)

Single drug	Common name	Scientific name	Therapeutic uses
Anar	Pomegranate	*Punica granatum*	Rich in vitamin C and iron increases RBC production and reduces oxidative stress common in thalassemia.
Shahad	Honey	*Hibiscus abelmoschus*	Contains iron and antioxidants, and aids in RBC formation.
Choqandar	Beetroot	*Beta vulgaris*	High in iron, minerals, and vitamins; elevates blood hemoglobin levels; possesses antioxidant properties.
Anjeer	Fig	*Ficus carica*	Rich in iron, increases hemoglobin levels, supports RBC production, and is a good source of folate.
Mako	Black nightshade	*Solanum nigrum*	Acts as a blood purifier, aids in iron metabolism and storage, and protects RBCs from oxidative stress.
Chuhara /Khurma	Dates	*Phoenix dactylifera*	High iron content supports RBC production and prevents anemia.

2.2.1 Medicinal herbs with high iron contents used in siddha medicine for thalassemia management

Highly iron-containing herbal medicines in the form of medicinal herbs are traditionally used in the Siddha modality to manage thalassemia. *Ficus racemosa* (Atti) is another wonder plant because of its abundance of iron and numerous healing properties. Other commonest ones are the pomegranate (*Punica granatum*) and dates (*Phoenix dactylifera*), which are especially rich in iron that increases hemoglobin through supplementation. Gooseberry is one of the

strongest vitamin C sources; it increases the absorption of iron and is expected to be effective. Sesame seeds (*Sesamum indicum*) are also among the main ingredients offering minerals, *e.g.,* iron. Moreover, Mookirattai keerai (*Boerhavia diffusa*) is credited for its blood manufacturing and state of well-being benefit as well. Together, these herbs form part of the classical Siddha method to address thalassemia-one way by withdrawing iron and promoting blood circulation (Devaki *et al.,* 2022).

2.3 Importance of herbal medicine in blood disorders

2.3.1 Herbs used to treat thalassemia

Herbal remedies that boost immunity, lessen weakness, and stop recurrent infections can be used to treat thalassemia symptoms. Giloy sattva, Moti pisti, Kaharava pisti, Pravala pisti, and Kumara-kalyana rasa are a few of the most often utilized herbs. Moti pisti promotes healthy protein formation and decreases the risk of thalassemia, whereas Giloy sattva aids in the prevention of blood diseases and the generation of red blood cells. While pravala pisti increases protein synthesis, strengthens the immune system, and decreases frailty, kaharava pisti encourages healthy blood flow. Thalassemia symptoms, red blood cell production, energy, weakness, and recurrent infections can all be eliminated with kumara kalyana rasa, a natural therapy (Li *et al.,* 2011).

2.3.2 Herbs used to treat anemia

Anemia is caused by yellow dock root, a wild vegetable rich in phytonutrients such as anthraquinonoid glycosides, tannins, oxalates, and resins. Adequate amounts of calcium, phosphorus, vitamin A, and vitamin C are also present (Latif *et al.,* 2022). Stinging nettle (*Urtica dioica*) is a medicinal herb that is actively consumed by anemic patients and helps with physical or mental fatigue (Fatima *et al.,* 2018). In botany, dandelion and burdock (*Taraxacum officinale* and *Artium lappa*) work together to improve the absorption of iron from food and have synergistic effects when used together to treat anemia (Kumar, 2024). Although, Parsley and Dang quay are useful in treating anemia, their blood-thinning qualities make them unsuitable for use by surgical patients (Gao *et al.,* 2018). Fenugreek (*Trigonella foenum*-graecum) is essentially very beneficial for girls who are anemic. The leaves have the capacity to keep the body's blood volume stable (Chourasiya *et al.,* 2019).

3. Indian medicinal plants with therapeutic potential

3.1 Plants that possess hematological characteristics

Compared with chemical consumption, medical plants have fewer side effects and are more suitable for the body's organisms. They contain antioxidants that improve blood, prevent free radical damage, and protect the red blood cell membrane. Certain plants can improve anemia, treat stomach ulcers and erythropoiesis and increase iron absorption. In thalassemia, the following medicinal plants are used: *Citrus latifolia* (Persian lime*), Ficus carica* (Fig), *Solanum tuberosum* L. (Potato), *Ananas comosus* (Pineapple), *Urtica dioica* (Stinging nettle), *Daucus carota* (wild carrot), *Solanum lycopersicum* (tomato), *Brassica rapa* (Mustard), *Rheum officinale* (Chinese rhubarb), *Foeniculum vulgare* (fennel), and Petroselinum *crispum* (parsley) (Cheraghi *et al.,* 2016).

3.2 Plants with antioxidant and anti-inflammatory effects

3.2.1 Natural antioxidants for treating iron overload

Natural antioxidants such as curcumin and grape seed extract (GSE) can aid in the treatment of iron excess. The polyphenolic components found in GSE extracts bind metals such as iron and neutralize free radicals (Guo *et al.,* 1996; Apak *et al.,* 2004). They can either increase hemic iron absorption on the apical side or inhibit intestinal absorption of nonchemical iron (Kim *et al*., 2008). Turmeric contains a low molecular weight polyphenol called curcumin, which has been demonstrated to increase the levels of transferrin receptor 1 and activate iron regulatory proteins while lowering hepatic ferritin levels (Jiao *et al.,* 2006). Curcumin at 1000 mg iron/kg body weight can increase TfR1 and iron-responsive element-binding protein levels, lower iron levels in the spleen and bone marrow, and promote the formation of hypochromic red blood cells (Jiao *et al.,* 2009). Onions, spinach, garlic, broccoli, black tea, tomatoes, and apples are rich sources of quercetin, flavonols with anti-inflammatory and antioxidant qualities (Hämäläinen *et al*., 2007). It may have an impact on iron homeostasis and aid in the defense of cells against oxidative damage (Lesjak *et al.,* 2019).

3.2.2 Natural antioxidants for thalassemia treatment

Iron overload-induced oxidative stress may be mitigated by flavonoids and phenolic substances, including polyphenols (Jomova *et al.,* 2011). Silymarin, a strong antioxidant with hepatoprotective and iron-chelating qualities, is derived from Silybum marianum (Gazak *et al.,* 2007). Clinical trials have employed it as an adjuvant with no adverse effects (Darvishi Khezri *et al.,* 2016). Desferioxamine and silymarin together are well tolerated and effective in promoting a decrease in iron and ferritin levels, increasing RBC GSH levels, and lowering serum ferritin levels (Gharagozloo *et al.,* 2013).

3.2.3 Plants with anti-inflammatory properties

Iron chelation therapy can be used to treat thalassemia, a common illness characterized by excess iron. One of the main phenolic compounds of turmeric, curcumin (Chuengsamarn *et al.,* 2012), has antioxidant, anti-inflammatory, and iron-chelating qualities. *C. sappan* is a traditional medicinal herb that has been utilized for its antibacterial, immunomodulatory, inflammatory-reducing, hypoglycemic, chemotherapeutic, and free radical scavenging activities (Lin *et al.,* 2014; Seo *et al.,* 2019). Bioactive substances such as phenols, flavonoids, polysaccharides, terpenes, gingerols, paradols and shogaols are found in ginger, spice and herbal treatment (Mao *et al.,* 2019). Gingerly is a safe drug because of its antibacterial, anti-inflammatory, anticancer, and antioxidant qualities (Nile *et al.,* 2015).

3.3 Iron chelation and detoxification potential of herbal compounds

3.3.1 Iron chelation therapy using herbal compounds

A major concern in thalassemia is iron overload as a result of excess intestinal iron absorption. Conventional iron chelators include deferoxamine (and R) deferasirox and deferiprone, all of which are associated with side effects such as gastrointestinal disturbances and nephrotoxicity (Cianciulli, 2009). This has led to an interest in natural iron-chelating herbal compounds. Various medicinal plants possess bioactive constituents, such as flavonoids, polyphenols, alkaloids and tannins that can chelate iron (Table 1) and are

antioxidants. Herbal iron chelators: The main key herbs with iron chelating effects and antioxidant capabilities are *P. emblica* (Amla), *T. chebula* (Haritaki), *C. longa* (Turmeric), *S. marianum* (Milk thistle), and *C. sinensis* (the natural caffeine) for lowering bioavailability from oral iron and protecting against iron-mediated oxidative damage (Husain *et al.,* 2023).

3.3.2 Detoxifying potential of herbal compounds

Curcumin is utilized as a healthy spice and in traditional herbal medicines as a hydrogen donor, antioxidant, and free radical scavenger. It has been shown to stop the development and progression of several diseases, such as cancer of the colon and pancreas, myelodysplastic syndromes, and multiple myeloma (Hatcher *et al.,* 2008). Iron chelation may enhance the anticancer properties of curcumin (Jiao *et al.,* 2009). Garlic and onions can be used as alternative remediation methods to improve the removal of harmful heavy metals such as arsenic, lead, iron, and mercury. They contain vitamin B6, manganese, and vitamin C, which may aid in the detoxification of heavy metals (Senapati *et al.,* 2001). Milk thistles, also known as *Silybum marianum*, contain flavonoids such as silybin, silydianin, silychristin, and 2, 3 dehydro derivatives (Borsari *et al.,* 2001). Oral consumption of silybin can shield the liver from iron-induced damage and reduce liver function impairments. In terms of its bioavailability, silybin appears to have the capacity to increase heavy metal excretion (De Smet *et al.,* 1992). Triphala, an ancient Ayurvedic herbal formulation, has antibacterial, anti-inflammatory, and antidiarrheal properties (Belapurkar *et al.,* 2014). The elimination of heavy metals relies on the regulation of gastrointestinal motility, which this traditional formula can support. *Mucuna purines*, a natural antioxidant, have been shown to reduce Parkinson's disease symptoms and have no negative side effects, unlike the current prescription L-DOPA. *M. purines* demonstrate divalent iron-chelating action and prevent the oxidation of lipids and deoxyribose sugars (Dhanasekaran *et al.,* 2008).

4. Medicinal plants used in thalassemia management

Thalassemia symptoms can naturally be alleviated with herbs. Herbal medicines are safe and are meant for regular use. Herbs serve to revitalize the immune system. Herbs help reduce weakness and eliminate persistent infections as well. Healthy red blood cells are formed by herbal treatments. Herbal remedies for hemoglobinopathies, including sickle cell disease (SCD) and thalassemia, that could be useful have been recently identified by scientists. The Bergatene-containing extract of Aegle marmelos stimulated erythroid development and HbF induction in human leukemic K562 cells (Ng *et al.,* 2014).

4.1 *Terminalia chebula* Retz. (Haritaki)

Haritaki (*T. chebula*), is a well-known herb due to its anti-inflammatory, antioxidant, immunomodulating, and hemopoetic qualities. Haritaki lowers oxidative stress major concern in thalassemia caused by too much iron and hemolysis using tannins, flavonoids, polyphenols, and other bioactive molecules. Research also indicates that controlling iron overload from many blood transfusions using moderate iron-chelating properties might be helpful. Moreover, its effect on erythropoiesis contributes to the maintenance of hemoglobin levels and hence supports those with anemia. Haritaki is usually taken in powder, decoctions, or capsules that are occasionally combined with other herbs, such as Amla and Giloy, for greater effects. Although, its medicinal value appears to be significant, more clinical trials are needed to confirm its safety and effectiveness in thalassemia management (Kumath *et al.,* 2010).

4.2 *Phyllanthus emblica* Linn. (Amla)

Given its high nutrient content and medicinal qualities, amla is very important for anemia therapy. Amla improves iron absorption in the gut, which is essential for people suffering from iron deficiency anemia, and is among the richest natural sources of vitamin C. By transforming non-haem iron (available in plant-based foods) into a more absorbable form, vitamin C enhances red blood cell manufacturing and hemoglobin synthesis. Moreover, Amla is full of polyphenols, flavonoids, and tannins with potent antioxidant effects that shield red blood cells from oxidative harm, a frequently found feature in hemolytic and thalassemic anemia. Research has shown that Amla also helps to manage anemia by activating erythropoiesis (the creation of red cells). Fresh fruit, juice, or powder is typically eaten; Amla is frequently blended with iron-rich foods or herbal preparations, including *T. chebula* (Haritaki) and *T. cordifolia* (Giloy), for increased effects. Amla supports blood health, increases immunity, and decreases related exhaustion and debilitation; therefore, it should be taken regularly. However, clinical trials are needed to confirm its effectiveness in anemia therapy, which is difficult to perform (Charmkar *et al.,* 2017).

4.3 *Tinospora cordifolia* Willd. (Miers.) (Giloy)

An immunomodulating, anti-inflammatory, and hematopoietic agent, Giloy, is also well-known in Ayurvedic medicine, which adds to its value in anemia treatment. By stimulating the bone marrow, giloy increases erythropoiesis (the production of red blood cells), hence helping to increase hemoglobin levels and combat tiredness from anemia. By shielding red blood cells from free radical attack, their high level of antioxidant constituents helps to reduce oxidative stress, a frequent side effect in thalassemia and hemolytic anemia. Giloy is therefore beneficial for iron deficiency anemia since it has been shown to promote iron metabolism and enhance the body's capacity to utilize iron effectively. Moreover, these immunomodulating characteristics are fundamentally important for anemic patients at risk of infection. For added effects, capsules, juice, or a decoction of giloy combined with other iron-accelerating and blood-cleansing herbs, including Amla and Haritaki, are typically used. Although, it is highly effective in treating anemia, further studies are needed to validate its effectiveness (Ghatpande *et al.,* 2019).

4.4 *Withania somnifera* (L.) Dunal (Ashwagandha)

Owing to its powerful hematopoietic, antioxidant, anti-inflammatory, and immunomodulation properties, withania somnifera (ashwagandha) somewhat depends on thalassemia handling. Among patients with thalassemia, iron overload, oxidative pressure, and chronic anemia further aggravate disease severity. Ashwagandha has been shown to promote erythropoiesis (red blood cell production) by enhancing bone marrow function, thereby increasing hemoglobin levels and lowering thalassemia-related exhaustion. Its high antioxidant level counteracts the oxidative stress produced by free radicals and excess iron, hence protecting red blood cells from degeneration and lengthening their life. Ashwagandha also has some iron-chelating properties that could help to decrease iron overload, a major concern in patients with thalassemia undergoing repeated blood transfusions. Furthermore, acting as an adaptive agent, it helps to soothe stress

and inflammation, otherwise exacerbating signs of disease. Furthermore, thalassemia can be used to fight infections more effectively by way of immune system improvement something that Ashwagandha accomplished. In combination with other herbal products, including Amla and Giloy, which are commonly used to increase their curative properties, it is often accepted as a powder, capsule, or decoction. More studies are needed in thalassemia therapy and management to confirm its efficiency and safety because of early experiments outlining its probable benefits (Singh, 2018).

4.5 *Curcuma longa* L. (Turmeric)

As a well-liked medicinal plant with strong antioxidant, anti-inflammatory, and immunomodulatory properties, turmeric is a good complementary therapy for thalassemia management. The primary active ingredient in turmeric, curcumin, has been thoroughly studied for its ability to reduce oxidative stress since severe iron overload and hemolysis result in significant concern in thalassemia-related oxidative stress. Curcumin protects red blood cells against oxidative injury and lengthens their life by functioning as a good free radical scavenger. Its iron-chelating properties could also help reduce iron overload, a typical side effect observed in thalassemia patients receiving numerous blood transfusions. Thalassemia mostly manifests as chronic inflammation caused by immune dysregulation and iron toxicity; hence, the potent anti-inflammatory qualities of curcumin could help alleviate it. Furthermore, its immunomodulatory effect enhances the immune response and reduces the risk of infections in thalamic patients. Research suggests that curcumin may also support erythropoiesis (red blood cell production); therefore, ameliorating anemia intensity and increasing hemoglobin levels. Turmeric powder, capsules, or decoctions are traditionally consumed along with black pepper (Piperine) to increase its bioavailability. Although, turmeric appears to be a good thalassemia therapy, further clinical trials are needed to validate its ideal dosage and results (Keerthana *et al.,* 2021).

4.6 *Moringa oleifera* Lam. (Drumstick tree)

Thalassemia management can benefit from the immunomodulatory, hematopoietic, and antioxidative activity of *M. oleifera* (Drumstick tree), a very healthy medicinal plant. Moringa aids in fighting anemia by increasing red blood cell (RBC) production and increasing hemoglobin levels; it is rich in iron, vitamin C, folate, and necessary amino acids. Its high vitamin C content helps with iron absorption, which is vital for thalassemic patients since they frequently have iron metabolism problems. Furthermore, when loaded with flavonoids, polyphenols, and carotenoids, Moringa behaves as a strong antioxidant that helps to protect RBCs from the oxidative damage caused by too much iron and hemolysis. Mild iron chelating effects, which might help control iron overload, which is a major concern in regularly transfused thalassemia patients, are another important advantage of Moringa. Its anti-inflammatory properties assist in lowering chronic inflammation, which is frequent in thalassemia owing to iron toxicity and immune dysregulation. Moringa is also famous for fortifying the immune system and thus increasing the body's resistance to infections, which makes thalassemia sufferers prone to infection. Moringa is usually taken together with other medicinal herbs, such as Amla and Giloy, to improve its healing properties; Moringa is usually eaten in powder, tea, capsules, or fresh leaves. Although, promising, more clinical studies are needed to determine its best dosage and long-term effectiveness in thalassemia treatment (Balebu *et al.,* 2023).

4.7 Other noteworthy medicinal plants

Fagonia cretica L., normally known as Dhamasa, is a family medicinal herb for its ability to reduce irritation and its advantages in terms of antioxidant traits. It is specifically useful for individuals with thalassemia and anemia, as it enables the defence of red blood cells from damage. In addition, it promotes the technology of excess crimson blood cells, referred to as erythropoiesis. Dhamasa can be used to modify iron levels, which is vital for individuals who require frequent blood transfers due to thalassemia. Historically, Dhamasa has been used in many methods, consisting of a drink, a powder, or natural tea, redecorating immune function and purifying blood (Seyal *et al.,* 2013).

Gundelia tournefortii L. is a lesser-seemed but effective medicinal plant with antioxidant, hepatoprotective, and anti-inflammatory effects. It is rich in polyphenols and flavonoids, which help combat oxidative strain and improve liver function, an essential problem for humans with iron overload because blood transfusions are not unusual. Additionally, its ability to detoxify homes can also be a useful resource for reducing the toxic effects of excessive iron deposition inside the frame (Mansi *et al.,* 2020).

Camellia sinensis (L.) Kuntze (green tea) is famous for its excessive catechins and polyphenol content, making it an effective antioxidant and mild iron chelator. In thalassemia control, green tea decreases iron toxicity and oxidative pressure, shielding RBCs from harm. Moreover, it allows cardiovascular and immune fitness, which might be essential for suffering from persistent anemia. The regular intake of tea has been associated with regular well-being advantages (Koonyosying *et al.,* 2020).

Silymarin (Milk thistle) is a broadly used hepatoprotective herb that is commonly recommended for liver health and detoxification. It consists of silybin and flavonolignans, which help protect the liver from iron-induced harm, which is the main feature of common transfusions for thalassemia patients. Furthermore, silymarin acts as an antioxidant, reducing oxidative pressure and helping conventional metabolic balance (Khezri *et al.,* 2016).

Andrographis paniculata (Burm.f.) Wall. ex Nees (Kalmegh) is an effective anti-inflammatory and hepatoprotective herb that has been traditionally used to aid liver characteristics and immune fitness. It includes andrographolides that have robust antioxidant and blood-purifying properties. This makes it useful for patients with iron overload, oxidative pressure, and immune imbalances. Additionally, its ability to beautify cleansing can also contribute to superior red blood health (Khare *et al.,* 2024).

Nigella sativa L. (Black seed) is a medicinal herb with anti-inflammatory, immunomodulatory, and hepatoprotective properties. Its active compound, thymoquinone, performs a sizeable function in reducing oxidative strain and enhancing immune features. *N. sativa* has historically been used to aid mobile health in purple blood and may be a useful resource for anemia management through improvements in hemoglobin levels. Moreover, it retains liver characteristics and is essential for iron overload in humans (El-Shanshory *et al.,* 2019).

5. Phytochemical and pharmacological aspects

5.1 Bioactive compounds responsible for therapeutic effects

Thalassemia treatment and management are possible because of the rich pool of bioactive compounds in Indian medicinal plants. Amla is purified from different flavonoid fractions containing quercetin yeine. rutin, rutin and arena catechins from *C. sinensis* (Green tea) as well as *P. emblica* (Amla), which has not been previously reported, and the *S. chebula* (Teheri haritaki) flavonoids and quercetin plant germplasm bank from agricultural. These reagents function as potent antioxidants that prevent oxidative stress in red blood cells (RBCs), which are a principal hemolytic factor in thalassaemia, to a very high degree. They also promote erythropoiesis (RBC production) and sequester excess iron, thus lessening toxicity from iron overload. Their mode of action is to increase the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase while simultaneously inhibiting lipid peroxidation in the RBC membrane.

Berberine, piperine and vasicine (alkaloid) are present in plants such as *B. herbidra* (S1), *Bushier nigrum* (black pepper) and *Adhatoda vasica* (Vasaka). These compounds are important for the synthesis of hemoglobin, especially during the induction of fetal hemoglobin (HbF), one of the compensatory strategies against the defective beta chains responsible for thalassemia. Moreover, alkaloids also have anti-inflammatory and liver protective effects that minimize chronic inflammation and prevent iron-induced liver dysfunction. Most notably, berberine increases HbF levels (mainly by increasing γ-globin gene expression), whereas piperine enhances the bioavailability of therapeutic compounds, increasing the efficacy of herbal treatments.

Tannins such as ellagic acid, gallic acid and chebulagic acid are included in *T. chebula* (Haritaki), *P. granatum* (Pomegranate) and *P. emblica* (Amla), which constitute another major group of bioactive compounds. Tannins are famous for their strong iron-chelating activity, which plays a significant role in sequestering excess iron and preventing its organ burden; thus, iron overload-related complications can be reduced. Tannins tans protect RBCs from oxidative stress-induced hemolysis, as they suppress the production of reactive oxygen (RMS) metabolites and stabilize RBC membranes, resulting in an extended lifespan.

Terpenoids (curcumin, glycyrrhizin and andrographolides), such as *Curculmonis longa* (turmeric), *Glycyrrhizin glabra* (licorice), *A. paniculata* (Kalmegh). The impact of these compounds is major, as they have anti-inflammatory, immunomodulatory and hepatoprotective effects on NF-κB inhibitors.

Dietary saponins, *e.g.,* diosgenin, ginsenosides and bacopasides, are present in *Asparagus racemosa* (Shatavari)/*Bacopa monnieri* (Brahmi) or *Panax ginseng* (Ginseng). The antihemolytic, iron-regulating and bioflavonoid effects of these compounds are well understood. In particular, diosgenin promotes the release of erythropoietin, which stimulates RBC production, whereas ginsenosides increase the activity of antioxidant enzymes to protect RBC cells from oxidative damage. Bacopasides influence iron transport proteins, which maintain a reduction in iron overload, ensuring homeostasis.

Polyphenols (resveratrol, epigallocatechin gallate (EGCG)) from grape by *Vitis vinifera* and *C. sinensis* (green tea). These compounds effectively alleviate oxidative stress and reduce iron overload and iron toxicity by binding excessive iron. Polyphenols are also beneficial to the heart, increasing the risk of thalassemia-related heart failure. Resveratrol activates the SIRT1 pathway, thus improving cellular defence mechanisms against oxidative stress; on the other hand, EGCG inhibits lipid peroxidation and retains RBC membrane integrity (Riaz *et al.,* 2023).

5.2 Mechanisms of action in thalassemia management

Table 3: Mechanism of phytochemicals involved in the treatment of thalassemia (Cotoraci *et al.,* 2021)

Mechanism	Phytochemicals involved	Effect
Iron chelation and detoxification	Tannins (ellagic acid, gallic acid), polyphenols (EGCG)	Binds excess iron, preventing toxicity.
Antioxidant activity	Flavonoids (quercetin, rutin), polyphenols (resveratrol)	Reduces oxidative stress, protecting RBCs.
Erythropoiesis stimulation	Alkaloids (berberine), saponins (diosgenin)	Enhances RBC production.
Hemoglobin synthesis regulation	Alkaloids (berberine, vasicine)	Induces fetal hemoglobin (HbF) production.
Liver and spleen protection	Terpenoids (curcumin, glycyrrhizin)	Prevents liver damage from iron overload.
Anti-inflammatory and immune modulation	Terpenoids (andrographolides), flavonoids	Reduces chronic inflammation in thalassemia.
Cardio protective effects	Polyphenols (resveratrol, EGCG)	Prevents iron-induced heart complications.

6. Preclinical and clinical research on medicinal plants

6.1 Experimental evidence from *in vitro* and *in vivo* studies

Several *in vivo* and *in vitro* studies have investigated the utility of herbal extracts for the production of fetal hemoglobin (HbF) and for relieving the oxidative stress caused by thalassaemia. A motivational effort was planned to investigate the *in vitro* effects of the ethanol extract of *Fructus trichosanthis* on the K562 erythroleukemia cell line. The results revealed that γ-globin mRNA expression and HbF production were increased by the extract. Multiple studies have suggested that the extract might potently activate p38 mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinase (ERK), indicating a potential therapeutic value for increasing HbF levels (Li *et al.,* 2011).In another study, the HbF-inducing activity of *A. vasica* extract (aqueous) was tested. These findings were confirmed by both *in vitro* studies where pyrroquinazoline alkaloids of the plant were shown to reversibly resensitize the γ-globin gene in a mouse model and enhance HbF formation without causing cytotoxi-

city. These *in vivo* studies further confirmed that it elicits increased HbF-ameliorating effects on blood precursor cells and biochemical parameters, enhancing *A. vasica*-mediated treatment of hematological lesions (Iftikhar *et al.,* 2022).

6.2 Clinical trials and human studies

Clinical investigations have also been carried out to investigate the effectiveness of herbal formulations in thalassemia patients. The traditional Chinese herbal medicine yisui shengxue granules (YSSXG) was used in a randomized controlled trial to study its effects on patients with β-thalassemia. The total study group included 60 patients, who were equally divided into two groups, one receiving YSSXG and the other receiving a placebo for three months. This judgment was based on the results of significant improvements in hemoglobin, red blood cell count, reticulocyte percentage and fetal hemoglobin percentages from baseline values in the YSSXG group. Additionally, the symptoms of hepatomegaly and splenomegaly improved, with no side effects, suggesting the clinical efficacy and safety of YSSXG in β-thalassemia treatment (Wu *et al.,* 2007).In addition, another clinical trial on erythropoiesis and oxidative stress was carried out with the FDA green tea epigallocatechin-3-gallate at an oral dose in a cohort of transfusion-dependent β-thalassemia patients. Treatment with EGCG reduced iron loading and modulated the expression of iron-specific proteins, leading to improved oxidative stability. These results indicate that green tea polyphenol EGCG might act as a beneficial adjuvant in thalassemia patients to reduce oxidative stress and increase the survival of red blood cells (Settakorn *et al.,* 2023).

7. Synergistic potential of herbal medicine with conventional therapies

Comprehensive attention has recently been given to the integration of herbal medicine with conventional therapies with the aims of improving treatment efficacy, reducing side effects and improving patient results. Many herbal medicines are rich in bioactive compounds that can work synergistically with modern drugs; therefore, they yield better therapeutic outcomes. Curcumin found in turmeric, for example, makes chemotherapy drugs, *e.g.,* paclitaxel, more effective in treating cancer. Ginger aids in the management of chemotherapy-related nausea, thus lowering the dependence on synthetic antiemetic drugs. From this perspective, herbal compounds have multitarget effects that act through several pathways, leading to a homogenous or holistic treatment paradigm. Despite these challenges necessitating the merging of herbal and conventional medicine (herb-drug interactions, a lack of regulation, inadequate quality control and delays in medical intervention, among others), an actual regulatory body such as the U.S. FDA or U.K. EMA is needed. Additionally, there is little formal education and training for herbal medicine among healthcare professionals, which makes incorporating herbal remedies in conventional practice challenging. Evidence-based research is vital for the safe and efficient integration of herbal therapy with conventional therapies. Regulatory and standardization efforts can enhance the quality control of herbal conventional combinations through the use of clinical trials to examine the efficacy safety profile and optimal dosage. The proper interactions between herbs and standardized pharmaceuticals must be understood to prevent potential drug-drug interactions. Successful examples of herbal-conventional synergy include turmeric enhancing chemotherapy outcomes, garlic aiding in blood pressure reduction (when combined with a diuretic), and berberine mimicking metformin in blood sugar regulation (Saghatelyan *et al.,* 2020).

8. Challenges in herbal-based thalassemia treatment

Thalassemia herbal treatments lack ample standardization, safety and regulatory acceptance. Geographical differences and variability in cultivation methods and postharvest processing may lead to variability in the content and bioavailability of herbal products, with associated quality control issues. The perception of "natural" equal's safety, toxicity and dosage problems stems from the common notion that natural substances are natively safe, yet the lack of defined and thoroughly studied safety profiles for most herbal medicines limits their safety. The potential to improve clinical data is further compromised by these variables. Barriers to regulation and acceptance include differences in world-backed regulations, the absence of rigorous control mechanisms, extremely poor compliance with quality manufacturing standards, incorrect labeling and unfounded therapeutic promises, which are all matters of public health. The unwillingness of traditional practitioners to communicate with scientific communities and the poor quality of clinical data also obstruct the uptake of herbal medicine into mainstream health systems (Dubale *et al.,* 2025).

9. Future prospects and research directions

Thalassemia paras' natural treatment: stringent scientific validation, drug discovery from Indian medicinal plants and integrated treatment regimes. The therapeutic use of traditional Indian medicine is great, but its global usage will come only through strong scientific validation. Information about Ayurvedic herbs should be recorded methodically and evaluated to ensure safety, efficacy, and quality. Integrative science can help move the journey from opinionated, anecdotal evidence to empirical data on either side of conventional healthcare. Indian medicinal plants provide a vast biochemical reservoir for other drugs, such as *Terminalia catapa*, which is characterized by its ability to stimulate fetal hemoglobin production *in vitro*. Integrative medicine modalities such as lifestyle changes, herbal remedies and a proper diet can improve the treatment of thalassemia. The integrative strategy supports an integrative care path with both physiological and lifestyle orientations in thalassemia patients (Mukherjee *et al.,* 2016; Chaachouay *et al.,* 2024).

10. Conclusion

Treatment of thalassaemia and its variants with medicinal plants of Indian origin: Possibilities and potentials operating through hemato-poietic, antioxidant and chelating iron. For a long time, traditional systems, *i.e.,* Ayurveda, Siddha and Unani herbal remedies, have been known to increase hemoglobin, iron regulatory and redox modulating properties, all of which are important in thalassemia management. This herb has been extensively characterized in the scientific literature to evaluate its rich potential as a therapeutic for *P. emblica* (Amla), *T. chebula* (Haritaki), *C. longa* (Turmeric) and *S. marianum* (Milk Thistle). Numerous studies have proven, at the *in vitro* and *in vivo* levels, that these plants possess bioactive compounds such as flavonoids, polyphenolic compounds, tannins and alkaloids that aid in erythropoiesis and the induction of natural iron chelation to protect against the oxidative stress-induced by iron. These compounds have been further confirmed by clinical studies in which herbal extracts (such as silymarin and curcumin) were used to reduce iron overload and improve overall patient outcomes. Despite the

medicinal potential of these plants, several obstacles, such as a lack of standardization in herbal formulations, considerations related to bioavailability and dose-response mechanisms, and regulatory hurdles, impede their large-scale clinical application. Solving these bottlenecks will require robust scientific support from a large-scale clinical trial that is ready to administer drugs with advanced formulations and herbal therapies integrated with conventional medicine. In the future, research efforts should be directed toward obtaining certified, safe and efficacious plant-based approaches that constitute optimal medical strategies. Indian medicinal plants can fulfil this clinical need, and at the same time, a biological gap between traditional knowledge and modern medical advancements may provide an idealistic solution by bridging this gap only in Indian thalassemia or other diseases.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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