

## **Nanotechnology-Based Management of Beta-Thalassemia: Exploring Curcumin as a Promising Therapeutic Agent**

### **Abstract**

**Background:** Beta-thalassemia is a group of inherited blood disorders characterized by decreased Hb production which leads to anemia and body does not have healthy RBCs do individual need regular blood transfusion. These transfusions do, however, frequently result in side effects including iron excess. A polyphenol called curcumin has anti-inflammatory effects and can raise the body's level of antioxidants. The use of nano-curcumin has shown a better treatment option for beta-thalassemia conditions.

**Objective:** The review was to evaluate the better treatment option for beta-thalassemia condition using nano-curcumin as a therapeutic tool.

**Method:** A comprehensive search to identify the relevant studies was conducted in online databases mainly Google Scholar, PubMed, Embase, Scopus. Around 100 articles were identified and after title and abstract review, 23 studies were included in the review.

**Conclusion:** Nanotechnology-based diagnostics, including biosensors and nano-biosensors, hold promise for early detection and monitoring of beta-thalassemia. Curcumin mitigate oxidative stress, reduce inflammation, and potentially alleviate the damage to beta-thalamic RBCs. However, the bioavailability of curcumin remains a challenge, and strategies to enhance its delivery and stability need to be investigated.

**Keywords:** Beta-thalassemia, curcumin, nanotechnology.

### **Introduction:**

Beta-thalassemia is a blood disorder that affects the production of hemoglobin, the protein responsible for transporting oxygen throughout the body. It is caused by a mutation in the gene that controls the production of hemoglobin beta globin chains. Beta-thalassemia causes decreased or no beta-globin production, resulting in a deficiency of alpha and beta-globin chains followed by the formation of abnormal red blood cells. The severity of beta-thalassemia can range from mild symptoms to life-threatening complications due to genetic mutation. This disease usually occurs in people of Mediterranean, Middle Eastern and Asian descent. [1]

Treatment for beta-thalassemia usually includes regular blood transfusions and iron chelation therapy to control excess iron from the transplant. Continuing research aims to develop new methods, such as nanotechnology-based interventions, to improve the management and treatment of beta-thalassemia.

Nanotechnology plays an important role in the management of beta-thalassemia by providing new solutions in drug delivery, gene therapy and diagnostics. Nanoscale drug delivery, such as nanoparticles and liposomes, improve the targeted delivery of medicinal drugs, increase efficacy and reduce side effects. Nanoparticles can also be used as a delivery vehicle for gene therapy that

deliver copies of the beta globin gene or modulate gene expression to restore the balance between alpha and beta globin chains. [2] Nanotechnology-based diagnostic tools such as nanosensors and nanobiosensors enable early and accurate detection of  $\beta$ -thalassemia biomarkers and help monitor disease progression and treatment response. In addition, nanotechnology facilitates the development of iron chelation to control excess iron through regular blood transfusions. Overall, nanotechnology offers promising strategies to improve the management and treatment of  $\beta$ -thalassemia. [2]

Curcumin, a natural compound found in turmeric, has been studied for its therapeutic potential for many diseases such as beta-thalassemia. [3]. Some studies suggest that curcumin may have beneficial effects on red blood cells in beta-thalassemia, including antioxidant and anti-inflammatory properties. Beta-thalassemia is associated with oxidative stress and inflammation, which can increase red blood cells. The antioxidant properties of curcumin may help reduce oxidative stress and reduce damage caused by reactive oxygen species. Additionally, curcumin has been shown to have anti-inflammatory properties and can reduce inflammation that damages red blood cells. [4]

In some studies curcumin has been reported to have potential iron chelating properties. In beta-thalassemia, frequent blood transfusions can cause excess iron, which can lead to further complications. Curcumin's ability to chelate iron may help reduce iron overload and its associated effects. [4, 5]

However, it is worth noting that curcumin has a low bioavailability and is rapidly metabolized and excreted from the body. Researchers have explored many strategies to increase the bioavailability of curcumin, such as combining it with other compounds or using nanoparticle delivery systems.

### **Curcumin**

Curcumin, also known as 1, 7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, is a lipophilic compound with rapid cell membrane permeability. It is the main ingredient of *Curcuma longa* L. (commonly known as turmeric) and is found in many forms in plant extracts. A turmeric extract has three main components: Curcumin I (diferrolymethane / curcuminoids) make up about 75% of the extract, Curcumin II (demethoxycurcuminoids) 20% and Curcumin III (Bisdemethoxycurcumin) up to 5% of the extract. [6].

For centuries, turmeric has been used in medicine in China, India and Iran in the treatment of many diseases such as diabetes, liver disease, rheumatoid arthritis, atherosclerosis, infectious diseases and cancer, in the treatment of indigestion, bloating, stomach ulcers, blood and stomach pains, duodenal ulcer. Its therapeutic effect on many diseases has attracted extensive research. More importantly, curcumin has been shown in many studies to have antioxidant, anti-inflammatory, apoptosis-inducing and anti-angiogenic properties. It exerts its effects by modulating many targets in cellular pathways, allowing it to exert many therapeutic effects. [7, 8]

Given curcumin's poor bioavailability and selectivity, researchers have introduced and tested numerous analogues of this compound to evaluate their activities against known biological targets and improve their bioavailability, selectivity, and stability. Additionally, several strategies have been introduced to enhance curcumin's bioavailability, increase plasma concentration, and improve cellular permeability while also increasing resistance to metabolic processes. [9]

Among these strategies, the use of nanoparticles for targeted drug delivery has shown promise. Nanoparticles provide curcumin with prolonged circulation, improved permeability, and enhanced resistance to metabolic processes. This approach offers advantages such as longer retention in the body, increased concentration at the target site, and protection against premature degradation or elimination. [11, 12]

### **Curcumin Nanotechnology Approaches:**

Nanotechnology has gained significant recognition as a transformative technology with vast potential for the future. One area where nanotechnology holds immense promise is in the field of drug delivery, specifically through the utilization of nanoparticles. These nanoparticles offer exciting opportunities to enhance the bioavailability and solubility of lipophilic compounds like curcumin. [13]

Various types of nanoparticles, such as liposomes, polymeric nanoparticles, micelles, nanogels, niosomes, cyclodextrins, dendrimers, silvers, and solid lipids, have emerged as promising alternatives for delivering curcumin at therapeutic concentrations. [13] These nanoparticles have shown potential in addressing major challenges associated with curcumin, including low solubility, instability, poor bioavailability, and rapid metabolism. They have demonstrated efficacy in diverse applications such as cancer treatment, wound healing, Alzheimer's disease, epilepticus, ischemic diseases, inflammatory diseases. [31]

Isacchiet al. studied and reported the therapeutic benefits of artemisinin or novel liposomal compounds based on a combination of artemisinin and curcumin. They reported that only 7 days after the start of treatment with artemisinin alone, it began to reduce parasitemia and changed the blood affected by the antibiotic. In contrast, treatment of artemisinin loaded with the liposomal delivery system appears to have an immediate antimalarial effect, treating all malaria simultaneously after vaccination. In particular, artemisinin loaded with liposomal curcumin appeared to have the most definitive and potent therapeutic effect in a mouse model of malaria. [22]

The improved blood circulation of artemisinin loaded with liposomal curcumin suggests that these nanosystems could be used as viable vehicles for parasites. This potent formulation adds to the mechanism of action of artemisinin, which acts as a blood-separating agent during the human host's erythrocyte phase. Agarwal et al. also evaluated the acute effects of liposome-encapsulated curcumin on enhanced current electroshock seizures, pentylenetetrazole-induced seizures, and status epilepticus in rats. Liposome-encapsulated curcumin increased seizure recurrent and myoclonus, and most seizure delays in shock current and pentylenetetrazole-induced seizures, respectively. [22, 23]

### **Nanotechnology and beta-thalassemia**

Numerous studies have explored the potential of nanotechnology as a tool to manage beta-thalassemia, a genetic disorder characterized by abnormal hemoglobin production. One notable study by A. K. Singh et al. investigated the use of curcumin-coated nanoparticles, specifically designed to deliver curcumin to the bone marrow. This targeted delivery system has shown promising results by increasing hemoglobin production, which addresses the underlying cause of beta-thalassemia. [24, 25]

Another research effort focused on the use of nanoparticles as carriers for deferiprone, a drug used to treat iron overload associated with beta-thalassemia. Compared to traditional methods, these nanoparticles have shown superior efficacy in delivering deferiprone. In addition, they showed a

reduced incidence of side effects, making them a potentially safer and more effective treatment option. [26],

These studies shed light on the potential of nanotechnology in the treatment of beta-thalassemia. By using nanoparticles as transport vehicles, targeted delivery of drugs to affected tissues or cells is possible, which improves treatment results. However, it is important to emphasize that further research is needed to validate these initial findings and expand the range of drugs that can be delivered using nanoparticles to specific cells involved in beta-thalassemia.

### **The mechanism of curcumin's action on beta-thalassemia cells**

A study conducted by Banerjee, S. et. al showed various effects of curcumin on beta-thalassemia cells mainly.

**1. Anti-Inflammatory Effects:** Beta-thalassemia is associated with chronic inflammation due to ineffective erythropoiesis and hemolysis, leading to the release of pro-inflammatory cytokines and mediators. Curcumin exerts its anti-inflammatory effects through multiple mechanisms:

**a. Inhibition of NF- $\kappa$ B:** Curcumin blocks the activation of nuclear factor-kappa B (NF- $\kappa$ B), a key transcription factor that regulates the expression of inflammatory genes. By doing so, curcumin reduces the production of pro-inflammatory cytokines like interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6).

**b. Modulation of MAPK Pathway:** Curcumin can interfere with the mitogen-activated protein kinase (MAPK) signaling pathway, which regulates various cellular responses, including inflammation. By inhibiting MAPK signaling, curcumin dampens the inflammatory cascade.

**c. Suppression of COX-2 and iNOS:** Curcumin downregulates the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), enzymes involved in the production of inflammatory prostaglandins and nitric oxide, respectively.

**2. Antioxidant Effects:** In beta-thalassemia, there is an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, leading to oxidative stress. Curcumin acts as a potent antioxidant to counteract oxidative damage:

**a. Scavenging of ROS:** Curcumin possesses free radical scavenging properties, neutralizing harmful ROS and preventing oxidative damage to cellular components.

**b. Upregulation of Antioxidant Enzymes:** Curcumin can upregulate endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, enhancing the cellular defense against oxidative stress.

**c. Metal Chelation:** Curcumin can chelate transition metals, such as iron and copper, which catalyze the formation of ROS. By sequestering these metals, curcumin reduces their participation in oxidative reactions.

**3. Iron-Chelating Effects:** In beta-thalassemia, excessive iron absorption and ineffective erythropoiesis contribute to iron overload. Curcumin exhibits iron-chelating properties that help in reducing iron burden by:

**a. Iron Chelation:** Curcumin can form stable complexes with iron ions, promoting their excretion and limiting iron toxicity.

**b. Downregulation of Iron Transporters:** Curcumin can decrease the expression of iron transporters, such as divalent metal transporter 1 (DMT1) and transferrin receptor 1 (TfR1), reducing iron uptake by cells.

**4. Induction of Fetal Hemoglobin (HbF) Expression:** Fetal hemoglobin (HbF) production in beta-thalassemia patients can ameliorate the severity of the disease. Curcumin has been shown to induce HbF expression through the activation of  $\gamma$ -globin gene transcription, offering a potential therapeutic strategy.

Overall, curcumin's multi-faceted properties, including its anti-inflammatory, antioxidant, and iron-chelating effects, make it a promising therapeutic agent for beta-thalassemia. By targeting various pathological pathways, curcumin has the potential to mitigate oxidative stress, inflammation, and iron overload in beta-thalassemia cells, ultimately improving disease outcomes. [4, 35]

One more study conducted by Ahmad, M. et. al concluded that the effect of curcumin on beta cells as Curcumin contains multiple functional groups, including phenolic hydroxyl and carbonyl groups, which enable it to chelate metal ions such as iron. In the presence of iron ions ( $Fe^{2+}$  or  $Fe^{3+}$ ), curcumin forms coordination bonds with iron, leading to the formation of a curcumin-iron complex and the functional groups in curcumin, particularly the phenolic hydroxyl groups, can coordinate with iron ions by donating electron pairs. This coordination involves the formation of bonds between the oxygen atoms of curcumin and the iron ion. The curcumin-iron complex stabilizes through chelation, forming a stable coordination compound. This complexation prevents the release of iron ions and hinders their participation in oxidative reactions, reducing the potential for iron-mediated damage.

**Reduction of Free Iron:** By forming stable complexes with iron, curcumin reduces the pool of free iron available for harmful reactions. Free iron can catalyze the production of reactive oxygen species (ROS) through Fenton and Haber-Weiss reactions, leading to oxidative stress and tissue damage. Curcumin's iron-chelating ability helps minimize these detrimental effects. Curcumin has been shown to facilitate the excretion of iron from cells and tissues. By chelating iron, curcumin promotes its removal through various pathways, including enhanced iron transporters and iron export systems.

Overall, the iron chelation mechanism of curcumin involves its ability to bind to iron ions, forming stable complexes and reducing the availability of free iron. This process helps mitigate iron-mediated oxidative damage and contributes to curcumin's potential therapeutic effects in conditions characterized by iron overload, such as beta-thalassemia. [36]

#### **Application of Nano-curcumin:**

Nano-curcumin is a form of curcumin that has been encapsulated in nanoparticles. This makes it more bioavailable, meaning that it can be absorbed more easily by the body. Curcumin is a natural compound that has antioxidant, anti-inflammatory, and anti-cancer properties. It has also been shown to be effective in treating a variety of other conditions, including arthritis, Alzheimer's disease, and cancer. [29]

In recent years, there has been growing interest in the potential use of nano-curcumin to treat beta-thalassemia. There is no cure for beta-thalassemia, but there are treatments that can help to manage the condition. These treatments include blood transfusions, iron chelation therapy, and bone marrow transplantation. However, these treatments can have side effects, and they do not cure the underlying condition. [32]

Nano-curcumin has been shown to be effective in improving the production of hemoglobin in beta-thalassemia patients. In one study, patients who received nano-curcumin showed a significant improvement in their hemoglobin levels, compared to patients who received a placebo. Nano-curcumin was also shown to be safe and well-tolerated by patients. These findings suggest that nano-curcumin may be a promising new treatment for beta-thalassemia. However, more research is needed to confirm these findings and to determine the long-term safety and efficacy of nano-curcumin in the treatment of beta-thalassemia.

#### **Some of the potential benefits of using nano-curcumin to treat beta-thalassemia:**

- Nano-curcumin is more bioavailable than curcumin, meaning that it can be absorbed more easily by the body. This could lead to better efficacy and fewer side effects.
- Nano-curcumin can target specific cells, such as red blood cells. This could improve the delivery of curcumin to the cells that need it most.
- Nano-curcumin is a safe and well-tolerated compound. This could make it a more attractive option for patients than other treatments for beta-thalassemia, such as blood transfusions and iron chelation therapy. [33, 34]

#### **Results:**

Nanotechnology offers promising strategies for beta-thalassemia management. Nano-sized drug delivery systems, such as nanoparticles and liposomes, provide enhanced delivery of therapeutic agents, improving their bioavailability and reducing side effects. Gene therapy using nanoparticles as carriers has shown potential for delivering healthy copies of the beta-globin gene and modulating gene expression. Nanotechnology-based diagnostics, including nanosensors and nano-biosensors, hold promise for early detection and monitoring of beta-thalassemia.

Curcumin, as a natural compound with antioxidant, anti-inflammatory, and potential iron-chelating properties, has been explored in the context of beta-thalassemia. Studies suggest that curcumin may mitigate oxidative stress, reduce inflammation, and potentially alleviate the damage to beta-thalamic RBCs. However, the bioavailability of curcumin remains a challenge, and strategies to enhance its delivery and stability are being investigated, such as nanoformulations and combination therapies.

#### **Conclusion:**

Nanotechnology-based approaches, including drug delivery systems, gene therapy, and diagnostics, offer promising avenues for the management of beta-thalassemia. Curcumin, with its potential therapeutic properties, holds promise as a complementary agent in the management of beta-thalassemia. Several key areas need to be addressed to optimize the potential of nanotechnology in the treatment of beta-thalassemia. First, the development of nanoparticles with enhanced stability, bioavailability and biocompatibility is essential. Surface modifications and coating techniques can

be explored to improve the performance of nanoparticles. Furthermore, comprehensive preclinical studies and rigorous clinical trials are necessary to assess the safety and efficacy of nanotechnology-based interventions in individuals with beta-thalassemia.

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