Journal of Pharmaceutical Research International

33(62A): 144-150, 2021; Article no.JPRI.80764
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Role of Curcumin in Beta Thalassemia: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i62A35161

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80764

Review Article

Received 24 October 2021
Accepted 27 December 2021
Published 28 December 2021

ABSTRACT

Beta-thalassemia is an inherited blood disorder characterized by defective beta chains of hemoglobin which often lead to the development of anemia. These patients require periodic blood transfusions to compensate for anemia. However, these transfusions often lead to complications such as iron overload. This abnormal hemoglobin can lead to anemia and cause other medical problems. Curcumin which is a polyphenol has anti-inflammatory properties and also can increase the number of antioxidants in the body. The main aim of the study is to determine the efficiency of curcumin in the treatment of β-Thalassemia.

The administration of curcumin in the treatment of β-Thalassemia has aided to be beneficial. Curcumin also exhibited hepatoprotective properties as serum bilirubin decreased in the β-Thalassemia patients. Supplementation of curcumin is seen to improve insulin resistance, lipid profile, and systemic inflammation by reducing HOMA-IR, TG, TG/HDL ratio, and hs-CRP levels. Curcumin when used in the treatment for β-Thalassemia showed low or no side effects. It has powerful anti-inflammatory effects and acts as a potent antioxidant where it can neutralize the free radicals due to its chemical structure.

Keywords: Curcumin; curcuminoids; beta-thalassemia; antioxidants; anti-inflammatory; innovation.

1. INTRODUCTION

β-Thalassemia major is autosomal recessive anemia, which is characterized by defective βglobin chain synthesis [1]. It is responsible for up to 50% of severe cases of β-thalassemia worldwide. Patients often require blood transfusions to compensate for low oxygen

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levels in the blood. However, these blood transfusions are not free from post-transfusion complications such as iron overload. Iron overload results from increased absorption of iron in the gastrointestinal tract and is greatly exacerbated by frequent transfusion therapy [2]. Patients with excessive iron often experience oxidative stress at intracellular and extracellular levels, leading to secondary complications such as anemia, hypercoagulability, hepatosplenomegaly, tissue injuries, and organ dysfunctions.

The primary treatment modality for iron overload in β-thalassemia major is iron chelation therapy [3,4]. Iron chelating therapies are necessary for overall survival without complications [5]. Several chelating drugs such as deferoxamine, deferiprone, or deferasirox were given daily to overcome the iron load. However, they are not free from adverse effects Besides, these are administered through a subcutaneous route which often results in poor adherence [6]. Recently several studies were conducted to evaluate the efficacy of curcumin alone or in combination with iron-chelating drugs to overcome the iron load complications. Curcumin (diferuloylmethane) is the most important phenolic compound of turmeric, the common household spice [7]. It is well known for its potential antioxidant, anti-inflammatory, anticancer, and iron-chelator properties. Curcumin has an iron-chelating property and could exert its insulin-sensitizing action by reducing the iron deposition and oxidative stress in thalassemia patients. However, there are conflicting reports of its beneficial effects in β-thalassemia major. Besides, most randomized controlled trial (RCTs) were carried out in small patients with diverse profiles. These studies found no or limited evidence of the beneficial effects of curcumin in these patients. However, animal studies had reported positive findings. Our team has extensive knowledge and research experience that has translated into high-quality publications [8-25]. Considering the limited and contrasting findings on the effects of curcumin in patients with β-thalassemia major. The aim of the study is to review the effect of curcumin in these patients.

2. CURCUMIN

Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are collectively known as curcuminoids [26]. These yellow-colored curcuminoids are isolated from *Curcuma longa* L. (turmeric) rhizomes, a plant species belonging to the Zingiberaceae family [27,28]. Turmeric is a plant known for its medicinal use, dating back to 4000 years ago in the Vedic culture in India, where it was used as a culinary spice and had some religious significance.

The curcumin International Union of Pure and Applied Chemistry (IUPAC) name is (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta69 1,6-diene-3,5-dione, also having the following synonyms: 1,7-Bis(4-hydroxy-3- 70 methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane, CAS number: 458-37-7 71 [29], UNII: IT942ZTH98 , Drugbank id: DB11672 , Einecs: 207-280-5 and 72 PubChem CID: 969516 [30].

Payton et al. [31] studied the typical representation of curcumin as a beta-diketone structure and confirms that it exhibits keto-enol tautomerism. As the main characteristics, this molecule has a molecular formula C21H20O6, molecular weight: 368.385 g/mol, melting point: 179–182°C, specific gravity: 0.9348 at 15°C, a log Kow of 3.29 (est) and appears as orange-yellow needles/crystalline powder. Apart from these, curcumin has 1) a variable solubility, i.e., insoluble in cold water and ether, soluble in alcohol and glacial acetic acid, and very soluble in ethanol and acetic acid; 2) good stability under recommended storage conditions (-20°C); and 3) a hazardous decomposition process under fire conditions, leading to the formation of toxic products (carbon oxides). Almeida et al. [32] also reported the physicochemical properties of curcuminoids. Prasad et al. [33] reviewed the pharmacokinetic parameters of curcumin, namely those related to delivery, bioavailability, absorption, and metabolism. The main concern with respect to curcumin, when exploiting its biological activity, is its bioavailability due to poor solubility, coupled with its poor absorption in plasma and tissues, rapid metabolism, and excretion, despite acting as a potent acid-base and boron indicator [34].

3. EFFICACY OF CURCUMIN

In the article done Pimpisid Koonyosying GTE-CUR drink promoted the uptake of plasma cholesterol through low-density-lipoprotein receptors-mediated endocytosis and also inhibited de novo synthesis of endogenous

cholesterol synthesis in the liver. The GTE-CUR drink could only induce small changes in the hematopoietic activity indicators during the study. Curcumin also decreases the levels of serum NTBI in thalassemia subjects with iron overload. It can also be noted that curcumin improved anemia and extramedullary hematopoiesis in the livers and spleens of tumor-bearing mice, which can also help in improving the quality and standard of human cancer patients [35].

In the study done by Ruchaneekorn Curcuminoids is a group of phenolic compounds of which are known for their antioxidant, anti-inflammatory, anti-cancer properties. It is said in this study that the mechanism of curcuminoids for scavenging free oxygen radicals and chelating NTBI is not known properly. The antioxidant property of curcumin shows that the percentage of MHb was significantly decreased, after administration of curcuminoids for 12 months, though there were no changes in Hb levels. It was also seen that the RBC GSH-Px activity gradually reduced during the treatment with curcuminoids and later returned to normal [36]. In the study done by Elahe Mohammadi, it is seen there is only limited evidence for the effects of curcumin on excess iron in β-thalassemia patients. Curcumin is a plant polyphenol that exerts iron-binding activity. Curcumin also has a synergistic effect on the iron-chelating property of deferoxamine through an iron shuttle [37].

A study done by Esmat Nasseri suggests that large doses of curcumin administration did not have any serious adverse effects. It is seen that Curcumin alleviates oxidative stress through several mechanisms. The β-diketone moiety and the hydroxy/methoxy groups on phenyl rings in curcumin are responsible for the direct radical scavenging property [38]. A study done by Jirawan Panachan reveals that antioxidant cocktails enhance their levels in beta-thalassemia patients' plasma. curcuminoids- and vitamin E cocktails significantly decreased iron-induced oxidative stress, increased Hb concentrations, and reduced hypercoagulability in β-thalassemia/Hb, also antioxidant cocktails improve anemia by the inhibitory effects of curcumin and glutathione on the complement system with unknown mechanism [39]. A study by Ahmad Tamaddoni suggests that Curcumin has an iron-chelating property and also exerted insulin-sensitizing action by reducing the iron deposition and oxidative stress in thalassemic patients. Curcumin is used as adjuvant therapy for attenuation of metabolic complications [40].

Curcumin can be useful for the relief of metabolic complications in such patients. β-Thalassemia patients require repeated blood transfusions, which causes oxidative stress due to elevated levels of highly reactive compounds and lipid peroxides and the reduction in TAC. Iron overload, the main complication of β-thalassemia major, results from increased absorption of iron in the gastrointestinal tract and is greatly exacerbated by frequent transfusion therapy [2]. Initially, the 12-week treatment plan with curcumin could not reduce Hb, serum iron, and ferritin levels. Previous animal research shows that for 6 months, dietary intervention with 0.2% curcumin in mice, iron level in liver and spleen decreased and mRNA of the L subunit of ferritin was down [41]. Many therapeutic properties of curcumin such as antioxidant, anti-cancer, and anti-inflammatory activity have been confirmed previously [42].

Curcumin on plasma protein expression was investigated using proteomic analysis in patients compared to normal subjects and in patients before and after supplementing with 500 mg curcumin daily for 12 months. Plasma proteins involved in blood coagulation and hemostasis are prothrombin, fibrinogen, and haptoglobin. These were decreased in patients, particularly in splenectomized patients. The administration of curcumin led to a significant increase in prothrombin, fibrinogen, and haptoglobin**.** Curcumin provides a protective effect on copper toxicity in thalassemia intermedia patients. It also shows that curcumin regulates zinc homeostasis which can be useful as a treatment method for patients with thalassemia intermedia, and especially in patients with zinc deficiency or low serum zinc/copper ratio [43].

Curcumin exhibits anti-inflammatory action through the suppression of numerous cell signaling pathways including NF-κB, STAT3, Nrf2, ROS, and COX-2. Curcumin is a highly potent antimicrobial agent. It is also synergistic with other nutraceuticals such as resveratrol, piperine, catechins, quercetin, and genistein [44]. The pleiotropic activities of curcumin have been modulated by various signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, cyclooxygenase-2, C-reactive protein, prostaglandin E2, prostate-specific antigen, adhesion molecules, phosphorylase kinase, AST,

and ALT, and many other molecules in human participants [45]. Extracts of green tea (GTE) and curcumin exhibit iron-chelating and antioxidant activities in iron-loaded cells and β-thalassemic mice [14]. The function of iron chelators is to remove excess iron from the plasma and the cells by binding the labile and chelate iron, thus facilitating its excretion through the urine and feces. Deferoxamine was the first iron chelator to be used clinically and is given via subcutaneous route overnight infusion through a portable pump. Its side effects are minimal, but its mode of administration results in low compliance [46]. Further studies are required to investigate the pathophysiological role of antioxidant cocktails which could improve the understanding of mechanisms and targets for the treatment of thalassemia.

This review shows that Curcumin is widely used in different parts of the world in the treatment of β-Thalassemia. Turmeric's bioactive ingredient is curcumin and the compounds related to curcumin. Curcumin and curcuminoids are excellent antioxidants. Antioxidants and iron chelators are found to be therapeutic in thalassemia. Curcumin administration in combination with deferoxamine has improved the antioxidant status in β-thalassemia major patients. They help to get rid of oxidative stress and excess iron. The easiest way to administer turmeric is the golden paste. This is a therapeutic version of dietary turmeric for the treatment of thalassemia.

4. CONCLUSION

Current treatment plans for thalassemia include blood transfusions and folate supplements which show certain side effects. Curcumin is poorly absorbed into the bloodstream, but when curcumin was used in the treatment for β-Thalassemia it showed low or no side effects. Curcumin is a natural herbal supplement that is derived from *Curcuma longa.* Curcumin exhibited powerful anti-inflammatory effects and a very strong antioxidant. Curcumin supplements mainly contain piperine, which increases the effectiveness. It is a potent antioxidant where it can neutralize free radicals because of its chemical structure. It can also boost the activity of our body's antioxidant enzymes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/80764