Labile plasma iron (LPI) as an indicator of chelatable plasma redox activity in iron-overloaded β-thalassemia/HbE patients treated with an oral chelator

Pensri Pootrakul, William Breuer, Matias Sametband, Pornpan Sirankapracha, Chaim Hershko, and Z. Ioav Cabantchik

Persistent levels of plasma nontransferrin bound iron (NTBI) have been associated with tissue iron overload and toxicity. We characterized NTBI’s susceptibility to deferoxamine (directly chelatable iron [DCI]) and redox activity (labile plasma iron [LPI]) during the course of long-term, continuous L1 (deferiprone) treatment of patients with hemoglobin E disease and β-thalassemia (n = 17). In 97% of serum samples (n = 267), the LPI levels were more than 0.4 μM (mean ± SEM, 3.1 ± 0.2 μM) and the percent transferrin (Tf) saturation more than 85 (111 ± 6), whereas only in 4% of sera were the LPI levels more than 0.4 μM for Tf saturation less than 85%. Daily administration of L1 (50 mg/kg) for 13 to 17 months caused both LPI and DCI to decrease from respective initial 5.1 ± 0.5 and 5.4 ± 0.6 μM to steady mean levels of 2.18 ± 0.24 and 2.81 ± 0.14 μM. The steady lowest levels of LPI and DCI were attained after 6 to 8 months, with a half time (t1/2) of 2 to 3 months. Serum ferritin and red cell membrane-associated iron followed a similar course but attained steady basal levels only after 10 to 12 months of continuous treatment, with a t1/2 of 5 to 7 months. These studies indicate that LPI and DCI can serve as early indicators of iron overload and as measures for the effectiveness of iron chelation in reducing potentially toxic iron in the plasma. (Blood. 2004;104: 1504-1510)

Introduction

Iron chelation therapy with deferoxamine (DFO) results in a significant improvement in the life expectancy of patients with transfusional iron overload. This is largely attributed to the prevention of heart disease in well-treated thalassemia major patients and, in a few, to the reversal of existing heart disease by aggressive DFO therapy.1,2 The orally active L1 (deferiprone) is more convenient for patients because, unlike DFO, it does not require a special transfusion pump or costly disposable infusers. Since its introduction in 1987,3 the orally active L1 has undergone clinical trials for treating thalassemia major patients.4,5 Although in some patients it might be as effective as DFO given subcutaneously, in others higher doses of DFO or combined therapy with L1 may be needed to provide adequate iron chelation.6

L1 seems to be particularly useful for patients with thalassemia intermedia, who accumulate iron at a much slower rate in the absence of transfusions. Early studies on those patients indicated a reduction in serum ferritin7 and liver iron stores8 following L1 treatment of up to 12 months. A more recent study of L1 has shown significant falls in serum ferritin and red cell membrane iron followed periodically over an 80-week period.9 Long-term treatment with L1 also led to a major reduction in end-point levels of liver iron and circulating forms of labile iron, collectively known as nontransferrin bound iron (NTBI),10 that are potentially harmful to the heart and other organs.

The present prospective study was undertaken with the aim of assessing the possibility that the basal levels of plasma NTBI could serve as early indicators of iron overload in iron-overloaded β-thalassemia/hemoglobin E (HbE) patients and of efficacy of chelation treatment with the oral chelator L1. In a broad sense, NTBI encompasses forms of iron that are not tightly associated with transferrin (Tf) or other proteins.10 Different detection methods exploited diverse properties of iron and probably measured overlapping subfractions of a larger iron pool collectively termed “NTBI.” We have focused on NTBI fractions in plasma or serum of iron-overloaded patients that are both labile—namely, redox active and chelatable—and refer to it as LPI, labile plasma iron. We determined NTBI at least 10 hours after the last dose of L1 was taken, to ensure that the measurements were not compromised by possible contamination with residual Fe chelates or, conversely, with residual free chelator. For that purpose, we applied 2 complementary assays. The first assay, DCI (directly chelatable iron), detects the NTBI component that is directly chelatable by DFO, as measured with a fluoresceinated derivative of DFO.11 DCI measures all the components of NTBI that are accessible to DFO, which includes endogenous ligands such as albumin and citrate as well as exogenous ones such as L1.11 The second assay, LPI, detects the fraction of NTBI that is redox active and eliminated by chelators such as L1 or DFO.12 Thus, in the absence of residual amounts of a chelator (eg, L1) or chelates (eg, L1-Fe complexes) in
the plasma, DCI and LPI should measure the same component of NTBI. The study was carried out over a 2-year period during which thalassemia intermedia patients were treated daily with 50 mg/kg L1 for up to 17 months and NTBI was followed periodically together with the more established markers of iron overload. The study indicates that periodic measures of LPI and DCI can serve as early indicators of the efficacy of chelation treatment.

**Patients, materials, and methods**

**Reagents**

The following materials were obtained and used without further purification: ascorbic acid, ferrous ammonium sulfate, bovine serum albumin fraction V (Sigma, St Louis, MO), dihydroxyamine 123, dihydrochloride salt (DHR) (Biotum, Hayward, CA), L1 (deferiprone; Apotex, Weston, ON, Canada), nitritotriacetic acid (NTA; Fluka, Seelze, Germany), deferoxamine (DFO) (Novartis, Basel, Switzerland), Chelex-100 chelating resin (Bio-Rad, Hercules, CA), and FL-DFO (N-(fluorescein-5-thiocarbamoyl) desferrioxamine; Molecular Probes, Eugene, OR). Iron-free HEPES-buffered saline (HBS; HEPES [N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid] 20 mM, NaCl 150 mM, pH 7.4) was obtained by treatment with 1 g per 100 mL. Chelex-100. Ascorbate (free acid form) was prepared as a concentrated stock of 20 mM in water. DHR (free acid form) was prepared as a concentrated stock of 20 mM in water. DHR fluorescence. In the LPI assay (Aferrix, Rehovot, Israel), each serum sample is tested under 2 conditions: with 40 μM DHR alone and with 40 μM ascorbate alone and with 40 μM ascorbate in the presence of 50 μM iron chelator. The difference in the rate of oxidation of DHR in the presence and absence of chelator represents the component of plasma NTBI that is redox active. The slopes (r) of DHR fluorescence intensity with time were calculated from measurements taken between 15 and 40 minutes. LPI calculation: Duplicate values of r in the presence of L1 (rL1), and in the absence of L1 (r0), were averaged, and the LPI concentration (μM) was determined from calibration curves relating the difference in slopes with and without L1 against Fe concentration as follows: LPI = Δr/r = (rL1 − r0)/r0, where Δr and r0 denote the L1-sensitive component of r and the calibration factor relating r to the Fe concentration, respectively. The calibration factor r0 was derived from calibration curves generated using iron concentration standards (0-20 μM) prepared in HBS containing 20 mg/mL bovine serum albumin, which were assayed for LPI similarly to serum samples.

Solutions for iron concentration standards were prepared from a stock solution of stable Fe(III)–NTA complex, formed by mixing equal volumes of 100 mM nitritotriacetic acid (NTA), titrated to pH 7.0 with NaOH, and 10 mM ferrous ammonium sulfate to produce a molar ratio of Fe/NTA of 1:10 and allowing the Fe(II) to oxidize to Fe(III) in ambient air for 30 minutes.

**Directly chelatable iron (DCI) component of NTBI**

The concentration of directly chelatable iron (DCI) in the sera of patients was determined with an assay obtained from Aferrix. The method, which was published previously,13 is based on the relative quenching of fluorescein-dFO by plasma NTBI. Calibration was carried out using the same iron concentration standards used in the LPI assay.

**Patient treatment and sampling**

Seventeen nontransfusion-dependent β-thalassemia/HbE patients from Thailand who were previously untreated (for at least 1 year) were engaged in the study over a 7- to 17-month period. The patients were recommended to take 50 mg/kg L1 (deferiprone; Apotex) daily in 2 doses, before or after meals. The patients were seen every week for the initial 3 months and then every month throughout the study for clinical examination and laboratory tests. Ophthalmic and auditory examinations were performed both before and at the end of the trial. A complete blood count and renal and liver function tests were performed on each monthly visit. Serum iron, total iron-binding capacity, ferritin, red cell membrane iron, LPI and DCI, and 24-hour urine were measured every 2 months. Serum samples were taken from the patients in the morning, at least 10 hours after the previous drug intake. A liver biopsy for liver iron estimation was performed at the beginning of deferiprone therapy, and the final biopsy was performed within 20 weeks of discontinuing deferiprone. Of the 17 patients, only 14 completed at least 15 weeks of treatment, some in a discontinuous fashion. The trial was approved by the Medical Ethical Committee of Mahidol University, Bangkok, and each of the patients gave full informed consent.

Statistical and graphic analyses were performed using the program Origin (version 7; OriginLab, Northampton, MA).

### Table 1. Parameters associated with iron overload in L1-treated patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial values</th>
<th>Final values</th>
<th>% change</th>
<th>t1/2 decay, mo, range</th>
<th>tmax decay, mo, range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver iron, mg/l</td>
<td>23.7 ± 4.3</td>
<td>11.4 ± 3.4</td>
<td>−52*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SI, μM</td>
<td>37 ± 19</td>
<td>36 ± 16</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tf sat, %</td>
<td>109 ± 23</td>
<td>107 ± 33</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SF, ng/mL</td>
<td>3352 ± 343</td>
<td>899 ± 599</td>
<td>−73*</td>
<td>4-6</td>
<td>10-12</td>
</tr>
<tr>
<td>RBCM iron, nmol/mg</td>
<td>37.2 ± 2.6</td>
<td>8.0 ± 1.5</td>
<td>−78*</td>
<td>3-5</td>
<td>10-12</td>
</tr>
<tr>
<td>LP1, μM</td>
<td>5.1 ± 0.5</td>
<td>2.2 ± 0.7</td>
<td>−57*</td>
<td>2-3</td>
<td>5-7</td>
</tr>
<tr>
<td>DCI, μM</td>
<td>5.4 ± 0.6</td>
<td>2.8 ± 0.2</td>
<td>−49*</td>
<td>2-3</td>
<td>5-7</td>
</tr>
<tr>
<td>EPO, UL</td>
<td>164 ± 43</td>
<td>264 ± 54</td>
<td>81*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hb level, g/L</td>
<td>66 ± 11</td>
<td>74 ± 11</td>
<td>12†</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

The table depicts the initial and final values of parameters associated with iron overload in 14 patients who completed a course of 13 to 17 months of treatment with L1 (50 mg/kg daily doses). The figures were taken from the analyses presented in Figures 2 to 4 and are depicted as mean ± SEM. The tmax decay indicates the time required to reach the lowest steady level for a given parameter; t1/2, the decay time to reach the half-maximum change; SI, total serum iron; Tf sat, %, percent transferrin saturation; and NA, nonapplicable.

*P < .01.
†No statistical significance.
It is clear from the table that whereas the percent transferrin saturation values and those of serum iron hardly changed over the L1 treatment period, all other iron serum parameters such as serum ferritin (SF), red blood cell membrane (RBCM) iron, LPI, DCI, as well as liver iron were reduced significantly by 50% to 80%.

Profiles of NTBI in L1-treated patients

The profiles of basal levels of LPI and DCI in 3 selected L1-treated patients are shown in Figure 1. The term “basal levels” is used to indicate that the samples, which were taken more than 10 hours after L1 administration, were relatively free of chelator and chelates, which presumably cleared from circulation. We based this assumption on the fact that LPI values, which reflect only labile iron, were very close to those of DCI, which detects both labile iron and L1 iron chelates. The profiles shown are representative of the different patterns observed. For each individual treatment, the trends obtained are not significantly different for both parameters, indicating a substantial degree of overlap exists between LPI and DCI. However, the values of neither parameter declined with time of treatment in a monotonous fashion. In some individuals the fluctuations were relatively higher than in others, possibly due to temporary (1 to 2 months) lack of full compliance and/or to intrinsic variations in iron utilization during chelation treatment. On the other hand, the hemoglobin levels of the treated individuals remained relatively stable or changed steadily (±20% to 30%) during the entire treatment, including the periods of highest fluctuations in LPI (P.P. and Z.L.C., unpublished observations, October 2003). This is also line with the fact that these patients did not undergo blood transfusions in the course of treatment. Much of the fluctuations were reduced by averaging the individual profiles at each time point (6- to 10-week periods), as shown in Figure 1D. Based on this paradigm, all the following profiles are given as mean values of parameters obtained from all the patients in the study in a given month or 2-month period.

The profiles of LPI and DCI (mean values ± SEM) obtained for the entire group of patients engaged in the study (n = 17) are shown as a function of duration of L1 treatment (Figure 2). After 6 to 8 months of daily treatment with 50 mg/kg, LPI reached basal levels of 2.2 ± 0.2 μM and DCI 2.8 ± 0.3 μM. The difference between LPI and DCI mean values was 0.3 to 0.6 μM over the entire profile and reflects probably the effects of various serum components on the assays—in particular, interference of radical

**Results**

Table 1 summarizes the parameters obtained in a 13- to 17-month follow-up study of 14 nontransfusion-dependent β-thalassemia/HbE patients from Thailand treated with 50 mg/kg daily doses of L1. Indicated are mean values of each parameter at the beginning and end of the study, the percent change of those values, as well as the length of treatment (t) required for attaining a final steady value and/or the maximum attainable change (t½) in the indicated parameter.
The inset yielded a slope of 0.011 

The half time of decline ($t_{1/2}$) was 1 to 2 months for LPI, 3 to 5 months for RBCM iron, and 4 to 6 months for SF.

**Discussion**

Nontransferrin bound iron (NTBI) has been detected in diseases associated with dysfunctions of iron metabolism caused by genetic factors or therapeutic interventions.\(^9\) The presence of NTBI in plasma has been assumed to be of potential risk to the heart and to...
The broken lines denote, for panels A and B, the value of 85 for percent Tf saturation; the correlations (corresponding mean ± SEM values for LPI (µM) versus the respective mean ± SEM values of either SF (nanograms per milliliter) (C) or RBCM (nanomoles per milligram of protein) (D). The correlations (corresponding mean ± SEM values plotted against each other) analyzed by the best linear fits yielded the following: (A) For LPI and RBCM iron (top); slope, 9 ± 1; intercept, \( -93 ± 3, r = 0.74 \); and (B) for LPI and SF (middle); slope, 660 ± 204; intercept, \( -100 ± 120, r = 0.78 \).

### Other Organs

Other organs due to its propensity for permeating cells by unregulated mechanisms and thereby causing iron overload and engaging in oxidative damage. Most of those studies have relied on models of iron overload obtained by imposing heavy loads of iron on animals with nonnatural sources of the metal or administering various types of iron salts into the medium of cultured cells. Although all of those maneuvers lead to global iron overload and ensuing tissue damage, they do not address the issue of NTBI’s involvement in organ damage in the clinical state.

To what extent the presence of NTBI in plasma has clinical implications depends, first and foremost, on whether or not it could be correlated with other clinical parameters associated with iron disorders. However, firstly, NTBI needs to be defined in clinical chemistry terms irrespective of its chemical composition. Originally NTBI was detected in sera from thalassemic patients as a chemical fraction of iron not associated with Tf. Attempts to improve the detection assays included the use of mobilizing agents in conjunction with chelators/detectors or high concentrations of ascorbate. The results indicated that NTBI is heterogeneous and variable not only quantitatively but also in composition, depending on the pathological condition in question. For example, in hereditary hemochromatosis, NTBI (0.4- to 3-µM levels) mobilized with agents such as nitritotriacetate or oxalate is detected in patients with Tf saturations lower than 85% and even as low as 55%, none of which is directly chelatable by agents such as DFO or L1 or by Tf itself. In thalassemia, unlike in hemochromatosis, NTBI levels span a wider range of values (0.4-10 µM), Tf saturation levels can reach 80% to 100% and even higher, and most of the NTBI is chelated by agents such as DFO or L1 by Tf itself. This fraction of NTBI, which in thalassemia is referred to as directly (or DFO-) chelatable iron (DCI), has recently been shown to be redox active and was therefore referred to as labile plasma iron (LPI). Regarding the chemical nature of NTBI per se, an early study carried out on serum from a hemochromatosis patient suggested citrate iron as the major NTBI component. However, that suggestion was probably not supported by data obtained by the same authors who showed that the putative component was barely accessible to DFO, whereas citrate Fe is readily chelated. Other candidates have been recently proposed but remain to be experimentally validated.

The present study was undertaken with the aim of assessing whether any of the labile forms of NTBI have clinical implications for iron overload conditions. Specifically, does NTBI represent a parameter that could be quantitatively correlated with established parameters of iron overload that also have diagnostic as well as therapeutic value and, if so, could it be used for assessing the efficacy of iron chelation therapy. We have chosen for this study a group of patients with overt iron overload and no previous treatment with chelator or recent (more than 2 years) blood transfusion who enrolled in a program of iron chelation therapy with L1. All patients had β-thalassemia intermedia or hemoglobin E disease. For NTBI measurements we applied both the DCI and the LPI methods, which in recent studies allowed the simultaneous detection of chelatable and labile iron in the plasma during treatment with L1. The measurements were carried out on blood samples withdrawn from patients at least 10 to 12 hours after the last intake of the drug to allow the NTBI to recover to “basal levels” following drug withdrawal. The study lasted for about 2 years in which 17 patients were treated daily with L1 (50 mg/kg in 2 doses), of whom 14 completed (cumulatively) 13 to 17 months of L1 treatment, with clinical and biochemical/hematologic tests taken monthly or bimonthly. A similar study showed recently that long-term treatment with L1 led to marked reductions in the final score of the biochemical/hematologic parameters, but no kinetic analysis was provided.

It is clear from Table 1 that, unlike serum iron and Tf saturation, the basal levels of DCI and LPI were reduced by L1 treatment to a similar extent (percent change) as liver iron, the classical parameter of iron overload. The final level of DCI or LPI observed after 13 to 17 months of treatment was already attained after 5 to 7 months, with a t½ of 2 to 3 months for either parameter. The decrease in LPI (Figure 4) and DCI (not shown) could be fitted to a single exponential decay function. On the other hand, the reduction in SF and RBCM iron levels was of a bimodal nature (Figure 4). The reduction in the last 2 parameters was detectable within 2 to 3 months of treatment (as LPI or DCI), but its second phase was more prolonged (10 to 12 months) (Figure 4). From the calculated t½ values and from the profiles shown in Figure 4, it can be deduced that the decrease in LPI preceded that of RBCM iron and in turn preceded that of SF. However, with presently available information, it is not possible to attach to the above temporal sequence any mechanistic linkage; nor is it possible to link LPI and liver iron, despite the results shown in Table 1. Nonetheless, the fact remains that substantial basal levels of liver iron and of both NTBI parameters LPI and DCI persisted in the plasma (2 to 3 µM) even when both SF and RBCM iron continued to decrease. This might be associated with the relatively mild regimen of L1 adopted (only 50 mg/kg daily), which might be sufficient for reducing SF and RBCM iron to relatively low levels but apparently is not sufficient for eliminating basal LPI or excess liver iron. Because the L1 concentration attained in plasma 2 to 3 hours after oral intake was still sufficient for complete elimination of LPI for at least 2 hours following administration of similar doses, it can be deduced that (1) LPI basal levels are steady-state levels of LPI that were replenished within 10 to 12 hours following drug intake and, if so,
(2) the LPI basal levels represent the balance between L1’s capacity for removing iron and the body’s for replenishing it. It should also be possible to establish a temporal correlation between LPI and body iron stores by quantifying changes in liver iron levels using noninvasive techniques such as magnetic resonance imaging (MRI) or a superconducting quantum interference device (SQUID) and correlating them with changes in LPI.

From the profiles depicted in Figures 1 and 2, it can be deduced that LPI and DCI are highly correlated; in some cases they are almost identical, and in others they differ at most by a value of 0.3 to 0.6 μM. Although that difference represents at most 25% lower values in LPI as compared with those of DCI, it is statistically different (P < .01). We tentatively attribute that difference to the possible presence of residual L1-Fe complexes that are detected by DCI as NTBI but not by the LPI assay or to presence of minor components of DCI that are not redox active.

The present studies offered the possibility of using the course of chelation as means to assess the parameters of iron overload with which changes in LPI could be compared—namely, percent Tf saturation and serum iron (Figure 2) and serum ferritin and the more recently identified parameter RBCM iron14 (Figure 5). In the group of patients treated for up to 17 months with L1, the average value of LPI (μM) in 267 samples was 3.1 ± 1.4 SEM and, of percent Tf saturation, 111 ± 12. The correlation between percent Tf saturation values and LPI is shown in Figure 5A. LPI levels higher than 0.4 μM, the threshold level found in a variety of iron overload conditions,12 were detected in 97% of the patients with Tf saturations higher than 85%. Similar results were obtained in patients with other forms of transfusion-induced hemodosisosis (W.B. and Z.I.C., unpublished observations, February 2004). In patients with Tf saturation values lower than 85%, only 4% had LPI at levels higher than 0.4 μM. This indicates that for most thalassemia intermedia patients whose average percent Tf saturation values were in the range of 87 to 116 (mean ± SEM, 108 ± 2), LPI was present only when Tf saturation exceeded 85% ± 5%. A similar picture was obtained for the correlation between SF and percent Tf saturation, except that only 75% of the samples had values higher than 85% Tf saturation and 750 ng/mL SF, and 17% had Tf saturations lower than 85% and SF levels higher than 720 ng/mL. It would appear paradoxical that SF (and RBCM iron) levels continued to decrease dramatically while Tf saturations decreased to a much lesser extent and remained high throughout the treatment period (Figure 5). One explanation for this discrepancy is that SF and Tf saturation represent iron pools with different rates of turnover and a much slower response to changes in the iron load. Thus, iron stores that induce secretion of ferritin into the circulation have a slow turnover (possibly days to weeks), while serum iron, and with it LPI and DCI, is replenished rapidly and continually within hours. Despite those differences between LPI and SF, which are also reflected in the decay profiles shown in Figure 4, these 2 parameters showed fair to good correlations (Figure 5C) as well as those between LPI and RBCM iron values (Figure 5D). The analysis indicates that for a particular treatment of daily L1 doses of 50 mg/kg, a decline of 9 nanomoles of iron per milligram of RBCM protein or 660 ng/mL SF was equivalent to a decline in 1 μM LPI.

In conclusion, NTBI assayed periodically as DCI and LPI or sequentially during treatment of thalassemia intermedia patients with L1 can serve not only as an early indicator of iron overload but also as a measure of the efficacy of the iron chelation treatment. Further studies remain to be conducted to establish whether the steady levels of LPI and liver iron attained even after prolonged treatment could be further reduced with higher doses of L1 alone or in combination with DFO. Recent observations obtained with thalassemia major patients in Italy treated with standard doses of either DFO given nightly (intravenously or subcutaneously), L1 (75 mg/kg/d) given orally 3 times during the day, or a combination of both (DFO nightly and L1 daily) indicate that only patients given combination therapy showed no detectable levels of LPI when followed 24 hours at 4- to 6-hour intervals (G. Zanninelli et al, manuscript in preparation).

To our knowledge, the present study is the first one in which an attempt has been made to correlate the effect of iron chelating therapy on LPI and DCI with conventional measures of iron overload such as serum ferritin, liver iron, and RBC membrane iron prospectively, over a period of 13 to 17 months. Our findings that the decrease in DCI and LPI is significantly faster than that of serum ferritin and RBC iron support the concept that LPI and DCI represent a labile and highly chelatable iron compartment with a rapid turnover. Furthermore, the sharp increase observed in the magnitude of LPI when transferrin saturation exceeds 85% indicates a threshold or overflow phenomenon wherein the harmful effects of iron overload are activated when iron accumulation exceeds a certain limit. Our conclusions are strongly supported by the recent studies of Jensen et al,29 in which threshold values of liver iron (more than 400 mmol/g dry weight), serum ferritin (more than 2500 ng/mL), and Tf saturation (more than 75%) have been found, beyond which hepatic and myocardial toxicity is regularly encountered in the form of increased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and abnormal myocardial iron concentrations. Conversely, the rapid decrease in DCI and LPI following the introduction of effective iron chelation therapy may imply early evidence of a beneficial protective effect to the heart, liver, and other vital organs. However, such correlations are yet to be found and require further prospective studies of well-documented clinical benefit.

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References


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