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RESEARCH ARTICLE

NATURAL AGENTS WITH IRON CHELATION POTENTIAL: A NEW HOPE AND PROMISE FOR CHEAPER SUPPLEMENT OF COSTLY IRON CHELATING MEDICINES FOR TRANSFUSION DEPENDENT THALASSAEMICS.

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Abstract

Thalassaemia is a blood-borne genetic disorder, which causes iron overload due to recurrent blood transfusions, especially in major and intermedia cases. Too much iron in the body is called iron overload. Iron overload is a condition characterized by the deposition of iron within the body (hemosiderosis). Symptoms of iron overload include: chronic fatigue, joint pain, abdominal pain, irregular heart rhythm, hair loss, skin color changes. So, along with blood transfusions, iron chelating drugs have to be administered in transfusion dependent major and intermedia patients with transfusional iron overload. But the common iron chelating drugs, available in market [DESFERAL (Desferroxamine), KELFER (Deferiprone), ASUNRA (Desferasirox)] has very costly for the economically backward patients and their family. At the same time, these market available drugs have very bad side effects, especially for long term use. In this review, we try to give a detailed account of all the natural agents, which have good iron chelating potential along with their sources. These natural agents are much less costly than the available drugs and being natural food agents, these will never show harmful side effects as the drugs show.

So, this paper will enlighten all concern people; clinicians, patients, health workers with natural agents as newer alternatives to costly iron chelating drugs with harmful side effects. Not only the natural agents will bring hope and promise to the patients who cannot afford cost iron chelating drugs, but also it attracts the pharmaceutical companies to promote research on these agents, extract active ingredients and formulate newer generation of iron chelating drugs at lower price and lesser side effects.

Introduction:-

Thalassaemia and Haemoglobinopathy are most common inherited non communicable genetic disorders in human and they represent as one of the major public health problem in many parts of the world including India (1). More than 100,000 babies worldwide are born each year with severe forms of thalassaemia (3). Thalassaemia occurs most frequently in people of Italian, Greek, Middle Eastern, Asian and African ancestry (4). It has been estimated that the prevalence of pathological haemoglobinopathies in India is 1.2 per 1,000 live births (5). Thalassaemia is genetic disorders that involve the decreased and defective production of hemoglobin, a molecule found inside all red blood cells (RBCs) that transports oxygen throughout the body (Miller, Thalassaemias, 2008). It is caused by alterations (mutations) in the genes that make globin proteins. Adult hemoglobin is made of two types of globin proteins: Alpha and beta. Thalassaemia occurs when there is a defect in a gene that helps control production of one of these proteins.

The standard of care for patients with thalassaemia major and intermedia is blood transtusion, regular follow up and iron chelation therapy. Thalassaemia major and intermedia patients are usually transfusion dependent and receive irregular transfusion when their hemoglobin levels drops below the normal level though these patients are liable to many complications; thalassemic faces, growth retardation, splenomegaly, hypersplenism, hypercoagulability, pulmonary hypertension, heart failure, cholelithiasis, diabetes mellitus, hypothyroidism, osteoporosis, and hypogonadism (7).

Iron overload is a threatening measure for transfusion dependent thalassaemia patients because there is no mechanism for the excretion of excessive iron and accumulated iron is responsible for elevated oxidative stress in biological system. Transfusion dependent thalassaemia, basically iron is accumulated in different organs, mainly, heart, liver, spleen, pituitary etc. and produces deadly damaging hydroxyl radicals in presence of superoxide or H2O2. Further, cellular constituents like lipid, protein, carbohydrate and nucleic acid are also damaged by this radical attack. The human body has no active mechanism for the excretion of iron (8).

In some patients, noticeably those with thalassaemia major, sickle cell disease, myelodysplastic syndrome, aplastic anemia, hemolytic anemia, and refractory-sideroblastic anemias, may become transfusion-dependent and receive excess iron with each transfusion (that the body has no means to excrete). Iron gradually accumulates in various tissues, causing morbidity and mortality. Each unit of transfused blood has approximately 250 mg of iron (9).

Thalassaemia and Iron Overload:-

Thalassaemia is a blood-borne genetic disorder, which causes iron overload due to recurrent blood transfusions, especially in major and intermedia cases. Too much iron in the body is called iron overload. Iron overload is a condition characterized by the deposition of iron within the body (hemosiderosis). Symptoms of iron overload include: chronic fatigue, joint pain, abdominal pain, irregular heart rhythm, hair loss, skin color changes. Organs cannot function normally with very high levels of iron (Table 1). Eventually, these organs become diseased. Below is a list of some of the proven diseases caused by too much iron in the body.

In transfusional iron overload (Table 2) the levels that can be controlled by normal iron homeostatic mechanisms, exceeds, leading to the formation of non-transferrin bound iron and subsequent cellular damage.

Along with the transfusional iron overload, abnormal iron metabolism also increases iron storage in the body, which is initially stored as Ferritin and deposited in organs as Haemosiderin, causing more toxicity to tissues. Transfusion dependent thalassaemia patients need blood transfusion quite frequently, which increases Ferritin level in these patients. So, search for efficient iron chelators is very important to decrease the iron overload in thalassaemia patients.

When iron overload occurs, transferrin becomes saturated, resulting in the presence of non-transferrin bound iron (NTBI) in the plasma. Tissue uptake of transferrin-bound iron is regulated and NTBI is taken up in an uncontrolled manner. This leads to pools of unbound iron within cells, which leads to the formation of reactive oxygen species (ROS). ROS react with cellular components leading to cellular leakage, dysfunction, and ultimately cell death. Iron is an essential micronutrient. But unbound or free iron can trigger free radical activity, which can also cause cell death, and destroy DNA. Free radicals are atoms or a group of atoms that have at least one unpaired electron. More stable and less reactive chemical structures as a rule have their electrons all paired to one another. Since this is not the case with free radicals, free radicals are constantly on the hunt for that additional electron and are highly reactive with other chemicals in the body. The free iron can catalyze the formation of very injurious compounds, such as the hydroxyl radical (-OH) from compounds such as hydrogen peroxide, which are normal metabolite byproducts. To remove accumulated iron, chelation therapy is thus recommended for patients with iron overload (Brittenham et al., 1994; Olivieri et al., 1994; Olivieri and Brittenham, 1997).

The primary goal of iron chelation therapies to prevent the accumulation of iron reaching harmful levels by matching iron intake from blood transfusion, with iron excreted by iron chelation (10). Children with severe thalassaemia, such as beta thalassaemia major, generally receive a transfusion every two to three weeks (11). Regular transfusions help keep hemoglobin levels near normal and help prevent many of the complications of thalassaemia. This treatment improves the child's growth and well-being and usually prevents heart failure and bone deformities. Individuals with beta thalassaemia major who are treated with regular blood transfusions and iron chelation often live 40 years or longer (3).

Children and adults with thalassaemia must undergo tests to measure the level of iron in their bodies. Blood tests are used to measure the amount of iron in the blood. Unfortunately, blood tests are not very accurate in measuring the levels of iron in the heart and liver. Providers may recommend a yearly liver biopsy, a surgical procedure in which a small amount of liver tissue is removed and tested. A few medical centers have begun to use new, noninvasive imaging tests called SQUID and T2* to measure iron levels in the liver and heart (2, 3, 11).

Some children with thalassaemia can be cured with a bone marrow transplant. However, this form of treatment is most successful when a donor who is an exact genetic match is available. Generally, a sibling or other family member is most likely to be an exact match. The procedure can cure about 85 percent of children who have a fully matched family donor (14). However, only about 30 percent of children with thalassaemia have a family member who is a suitable donor (11). The procedure is risky and can result in death. Recent studies suggest that using umbilical cord blood from a newborn sibling may be as effective as a bone marrow transplant (13). Like bone marrow, cord blood contains unspecialized cells called stem cells that produce all other blood cell. Several recent studies suggest that pregnancy appears safe for a woman with well-treated beta thalassaemia major who does not have heart problems (13, 14). Chelating drugs are usually stopped during pregnancy because it is not known whether they pose risks to the baby (11, 14).

In some disorders, such as β-thalassaemia, excessive intestinal absorption adds to the transfusion-induced iron overload. In thalassaemia intermedia, high erythropoietic drive causes hepcidin deficiency. The lack of hepcidin results in hyperabsorption of dietary iron and body iron overload. In thalassaemia major, transfusions decrease erythropoietic drive and increase the iron load, resulting in relatively higher hepcidin levels. In the presence of higher hepcidin levels, the dietary iron absorption is moderated and macrophages retain iron, but body iron stores increase due to the inability to excrete iron in transfused red blood cells (3).

When the plasma iron-binding protein transferrin is oversaturated, as in transfusion-induced iron overload, then the excess iron circulates as relatively free non–transferrin-bound iron (NTBI). Transferrin saturation can be easily measured and is a surrogate marker for NTBI, although this is far from perfect (23). Transferrin saturation above 50% is suggestive of a high iron load, but this is a dynamic number and may vary with inflammation.

This NTBI is rapidly taken up by liver and other tissues. Transferrin-bound iron (TBI) is also taken up by those cells through the hepcidin mechanism, which is increased in such states (15). It is this excessive iron that damages tissues.

A specific portion of NTBI is the chelatable labile plasma iron (LPI), which is not found in the healthy individuals (16). That is the most toxic component due to high reduction-oxidation (redox) potential that generates oxygen-free radicals such as superoxide anion in the cells, which damages DNA, proteins, and the membrane lipids in the cell (17).

NTBI and LPI are very specific for iron overload and have promising value as monitoring parameters for clinical response to chelation therapy (24). However, the lack of a standardized assay and limited data for general use for transfusion-induced iron overload makes it necessary to further investigate the use of NTBI and LPI. The Hepcidin measurements in serum and urine have been performed using mass spectrometry, and this may be a feasible marker in the future (25). The patient's complete blood cell (CBC) count should be monitored for the hemoglobin/ hematocrit to maintain a high threshold for transfusion. The degrees of iron deposition and fibrosis are higher in splenectomized and cirrhotic individuals than in non-splenectomized and non-cirrhotic patients (26).

Serum ferritin has been extensively used as an easily accessible serum marker for transfusion-induced iron overload. The ferritin level that has been used as a cutoff point for iron toxicity has varied in studies from 1000 ng/mL to 3000 ng/mL (18, 19).The major drawbacks of the ferritin are a lack of specificity and inter-patient variability (20).

Background Study (the scenario of present drugs):-

The primary goal of the iron chelating therapy is to prevent the accumulation of iron reaching harmful levels by matching iron intake from blood transfusion, with iron excreted by iron chelation (27). Although NTBI and liver deposits are chelatable to a degree, iron that is deposited in other organs such as the heart is not readily chelated, making cardiac failure a leading cause of death amongst those who undergo long-term transfusions (28).

The initiation of chelation therapy is a decision that has to be individualized. In general, transfusions exceeding 100 mL/kg of body weight are reasonable enough to merit thorough evaluation and probable initiation. Autopsy studies in the 1970s (29) and MRI data (30) obtained in recent years show that after 75 or more units of transfused blood, more than 50% of patients have excess iron in their myocardium. Thalassaemia involves the under production of hemoglobin, the indispensable molecule in red blood cells that carries oxygen. In order to survive, thalassaemia patients for all their life need regular blood transfusions every 3 weeks, daily drugs and regular iron chelation. To survive, a thalassaemia major patient must receive blood transfusions every 3 weeks during his or her life, and he or she also needs daily drugs and regular iron chelation therapy, to remove the excess of iron caused by the transfusions.

Available iron chelating drugs in market are DESFERAL (Desferroxamine), KELFER (Deferiprone), ASUNRA (Desferasirox).

Desferal (Desferroxamine):-
Desferrioxamine is an iron chelating agent. Its brand name is Desferal. One molecule of desferrioxamine binds one atom of iron forming a highly stable iron complex; thus, 1 gram of desferrioxamine could bind almost 93 mg of iron. However, in standard clinical use, only a small proportion (about 10%) of the drug binds iron before being eliminated from the body.

Desferal is not absorbed in the intestinal tract; this drug must be administered intravenously, which is done in an infusion center or hospital or subcutaneously, which is done using a portable battery-operated infusion pump.

Deferoxamine (DFO) has been used for more than 30 years for iron chelation. However, it is a drug that requires subcutaneous or intravenous infusions because of its short half-life and poor oral bioavailability, making compliance an issue (31). The early use of deferoxamine in an amount proportional to the transfusional iron load reduces the body iron burden and helps protect against diabetes mellitus, cardiac disease, and early death in patients with thalassaemia major (31). In nut shell the side effects of desferrioxamine includes costly, administered parentally, local irritation and swelling after subcutaneous infusion.

Kelfer (Deferiprone):-
Deferiprone is an orally active iron chelator which is currently being evaluated in clinical trials in several centres. It was originally licensed only in India, but has recently been licensed in Europe as second line therapy for patients unable to take desferrioxamine. Deferiprone may be considered as an alternative treatment. However, it should be emphasised that the long-term safety and efficacy of deferiprone are not yet known. The daily dose of deferiprone that has been evaluated most thoroughly is 75 mg/kg/day, given in three equally divided doses. Urinary iron excretion at this dose correlates with serum ferritin, generally achieving negative iron balance in heavily iron-loaded patients [Olivieri 1990]. The side effects of deferiprone include agranulocytosis, neutropenia and zinc deficiency in diabetic patients.

Asunra (Desferasirox):-
It is a very new oral chelator product in the market, much work not yet been done so far. But, it surely has many side effects. The side effects of desferasirox include nausea, vomiting, abdominal pain, diarrhea and skin rash. But the side effects vary from one patient to another.
The thalassaemia affected people are mostly from economically less solvent to spend the cost of the iron chelation drugs drugs for their blood transfusion dependent thalassaemia children. So, most of the child do not get the iron chelation drugs like DESFERAL (Desferroxamine), KELFER (Deferiprone), ASUNRA (Desferasirox) properly, just for the economic reason. Not only the economic reason, but also these available iron chelating drugs have bad side effects, especially for long term use.

Natural Agents with prospective iron chelation potential:-

There are two main approaches of iron chelating agents. The first is to supplement with nutrients that can bind up, or chelate the iron in molecular complexes. Chelation isolates iron from tissues and limits its ability to catalyze the oxidant reactions that damage them. Chelation also hastens excretion of excess iron from our body (32). Ultimately, it means that chelation limits our body's exposure to the destructive effects of iron accumulations.

The second approach to minimizing long-term iron damage is to optimize our antioxidant regimen. That can help us to prevent any further damage by iron's catalytic reactions with oxygen.

Some natural agents (Table 3) have strong iron chelating potential without producing side effects, like other chemical drugs, since these are parts of our natual diet. These are the following –

- Phytic acid (inositol hexaphosphate) from Rice Bran.
- Curcumin from Turmeric.
- Lactoferrin, Silymarin and Silibinin from Milk.
- Aestivum from Wheat Grass.
- Quercetin from Berries.
- Polyphenols from Cranberry and Pomegranate.
- Epigallocatechin-3-gallate or EGCG from Green tea extracts.

Phytic Acid from rice bran as iron chelator:-

Phytic acid (known as inositol hexakisphosphate (IP6) or phytate when in salt form) is the principal storage form of phosphorus in many plant tissues, especially bran and is unique among antioxidants because it both binds to iron and reduces the affinity of oxygen to hemoglobin. Rice bran is a by-product of rice processing industry, with high levels of phytic acid or phytate.(33) .

IP6 cleanses heavy metals IP6 attaches to heavy metals such as mercury, lead and cadmium, as well as loose iron, copper and calcium (35). IP6 is a selective chelator -- it does not attach to potassium, sodium or magnesium, important electrolyte minerals required for heart rhythm. IP6 does not remove calcium from bones or iron from red blood cells. Once chelated (attached), these excess minerals are excreted via the urinary tract (36).

Phytic acid (IP6), derived as an extract from rice bran, is the most potent natural iron chelator and has strong antibiotic and antioxidant action (37). IP6 has been found to have similar iron-chelating properties as desferrioxamine, a drug commonly used to kill germs, tumor cells or to remove undesirable minerals from the body (38).

Extensive studies have been conducted to confirm the lack of toxicity of IP6. In 1987, researcher Ernst Graf reported that only 4 of 22 chelating agents studied, including IP6, block hydroxyl radical production. Only phytic acid or IP6 was found to be economical, nontoxic, and effective (39).

There is a simple, economical and effective way of ridding the body of all of these undesirable organisms, debris and metals with advancing age --- IP6 rice bran extract. IP6 is known as nature's master mineral chelator (remover).

Curcumin from Tumeric as iron chelator:-

Curcumin is an effective chelating agent found naturally in turmeric. Curcumin is the major chemical component of the spice turmeric, which has multiple health benefits as an antioxidant and anti-inflammatory molecule (40, 41, 42). Curcumin may also be effective in the treatment of cancer because cancer cells are high in iron content. Unlike other drugs CURCUMIN does not have any side effects and show low toxicity. In addition to its direct chelation of iron, curcumin induces increased genetic expression of the body's natural iron-binding and transport protein, ferritin further sequestering iron away from vulnerable tissues (43). These multiple capabilities lead directly to reduction in iron levels in iron-overloaded organs (43, 44, 45, 46). Recently, it was discovered that curcumin's iron-chelating ability helps restore natural DNA repair mechanism (47).

Iron chelators repress ferritin translation, so, that curcumin may act as an iron chelator. Nontransferrin bound iron is found in plasma of β-thalassaemia patients which causes oxidative tissue damage leading to cardiac siderosis in β-thalassaemia patients. Curcuminoids can chelate plasma non-transferrin bound iron and leads to inhibition of lipid peroxidation to alleviate cardiac autonomic imbalance. Desferrioxamine, deferiprone and deferasirox all are promising chelators used to get negative iron balance and improve life quality. Deferiprone has been shown to remove myocardial iron effectively (48, 49). Curcumin contributes to in vitro removal of non-transferrin bound iron by deferiprone and desferrioxamine in thalassaemic plasma (50). Curcumin, a strong antioxidant and iron chelator, is to decrease oxidative stress in β-thal/HbE patients.

Lactoferin, Silymarin and Silibinin from milk as iron chelator:-

Lactoferrin, an effective iron chelator, binds to the Fe^{+} ions and decreases iron overload to the thalassaemic patients. Early work on milk thistle extracts basically focused on their antioxidant functions, but more recently evidence for potent iron chelation has been revealed as an additional liver-protective mechanism.(51, 52) Iron-overloaded animals can be protected from the liver fibrosis-inducing effects of iron by regular doses of silibinin, a milk thistle component (53,54). Impressive data for the impact of silibinin on iron-overloaded patients is now also available. In patients with chronic hepatitis C, in whom iron accumulations contribute to liver failure, treatment with a mixture of silibinin and soy complex resulted in a significant decrease in serum levels of ferritin, the iron-bound protein which reflects total body iron levels (55). Recent study shows, in patients with thalassaemia major, who have massive iron accumulations as a result of multiple transfusions, 140 mg three times per day of the milk thistle component silymarin enhanced iron-chelating effects of the drug desferrioxamine (56). This study shows the potential effect of Lactoferrin, Silymarin and Silibinin from milk on transfusion dependent thalassaemic patients, having iron overload.

Aestivum from Wheat grass as iron chelator:-

Triticum aestivum (wheat grass) is widely used in traditional medicine to treat various diseases. aestivum were established to have iron chelation potency and antioxidant activity (57). Researchers from India presented a study examining the effects of wheat grass as an iron chelator in transfusion-dependent myelodysplastic syndromes (MDS) patients on May 29 at the 2009 American Society of Clinical Oncology (ASCO) meeting.Patients with MDS or other transfusion-dependent diseases like Thalassaemia are at risk for toxic iron build-up in cells, and possible organ damage. Iron chelators bind to excess iron for removal from the body (58).

Quercetin from Berries as iron chelator:-

Flavonoids are naturally occurring plant molecules that offer both powerful antioxidant protection and the ability to bind to free iron atoms (32, 59, 60). Quercetin, which is a flavonoid found in berries and other plants, chelates iron atoms as powerfully as the prescription drugs used in managing severe cases of iron overdose (61,62). It's antioxidant effects are likely to be closely related to its strong iron-chelating capacity, and account for its ability to prevent the DNA strand damage that can precedes cancer development (63, 64).

Quercetin is included in properly formulated resveratrol supplements since it boosts resveratrol's beneficial effects in the body.

Polyphenols from Cranberry and Pomegranate as iron chelator:-

Dark-colored and red fruits are known to have many health benefits, in large part because of their high content of polyphenols. Cranberry and pomegranate, which extracts rich in polyphenols have now been shown to have potent iron-chelating capabilities, in some cases completely suppressing iron-catalyzed oxidant reactions (61, 65).
New evidences shows that another way cranberry extracts work is by depriving infecting bacteria of the iron they need for survival through chelation (66, 67).

Epigallocatechin-3-gallate/ EGCG, from Green tea extracts as iron chelator:-

After water, tea is the most commonly-consumed beverage in the whole world (68). Unfermented Green tea leaves have numerous health benefits, chiefly attributable to their content of a polyphenol molecule called epigallocatechin-3-gallate, or EGCG (69). EGCG is a well-known antioxidant (70). It was shown in recent years to powerfully chelate unbound iron and protect vulnerable tissues (71, 72).

Green tea extracts rich in EGCG bind to iron, and scientists already proposed their use as an alternative or adjunct to commercial iron chelators, which, while effective, may come with negative side effects (73, 74). Such drugs are used to treat thalassaemia, a condition which when severe enough, can cause massive iron accumulations as the result of frequent blood transfusions. EGCG from green tea has now been used safely and a well as effectively to bind and remove iron from the blood of individuals with thalassaemia (75, 76) and in studies of animals deliberately overloaded with iron to mimic aging, green tea extracts are able to bind free iron and reduce iron-related tissue oxidation in brain and liver tissue (67).

Discussion:-

At least 15 million blood units are required per year, and it is a relevant cost for the health-care system and an issue for the children and their families. In low-income countries, the great majority of children dies within the first year of age, because they can't afford the transfusions, and the ones who survive, they barely reach 15 years of age.

Since thalassaemia is mainly spread in developing countries and it almost affects poor people, the cost of the cure is too high for most of them. Many of the families that we work with are already in desperate or crisis situations so, when one or more of the family members get sick and/or require medical attention, the families often cannot afford to pay for their transport, food and other costs to get them the treatment they need. So, most of the patients need the cheaper alternatives than the costly iron chelating drugs. Two specific issues can be addressed well by these new natural agents with better iron chelation potentials. The first one is, thalassaemia affected people are mostly from economically less solvent to spend the cost of the iron chelation drugs for their blood transfusion dependent thalassaemia children. So, most of the child do not get the iron chelation drugs like DESFERAL (Desferroxamine), KELFER (Deferiprone), ASUNRA (Desferasirox) properly, just for the economic reason along after blood transfusion. So, if we can provide cheap, alternative natural food supplements which can function as potential iron chelator, will be very helpful for the poor transfusion dependent thalassaemia patents. The second one is, the available iron chelating drugs [DESFERAL (Desferroxamine), KELFER (Deferiprone), ASUNRA (Desferasirox)] have bad side effects. If new natural alternative food supplements can be found, which can function as potential iron chelator, will help to reduce the excess iron form the patients without side effects similar to the present drugs. At the same time, it continues to function as good iron chelator in patients with iron overload.

Tables:-

Table 1: Organ specific diseases due to excess iron

Organ	**Illness or Disease**
Liver	Cirrhosis, Liver cancer
Joints/Bones	Osteoarthritis,Osteopenia, Osteomalacia
Pancreas	Diabetes
Gallbladder	Gallstones
Heart	Irregular heartbeat, Heart attack
Skin	Bronze or Ashen Gray Green colour

Table 2: Estimates of transfusional Iron load.

Patient's weight	**35 Kg**	**50Kg**	**65Kg**
Total blood volume transfused (ml)	5830 - 11700	8330 - 16600	10800 - 21700
Transfusional Iron load (g/dl/year)	4.1 - 8.1	5.8 - 11.5	7.5 - 15.1

Table 3: Natural Iron Chelating Agents, their sources and chelating mechanism.

Name of the agent	Source	Role as Iron chelator	References
Phytic acid (inositol hexakisphosphate (IP6))	Rice Bran	IP6 is a selective chelator -- it does not attach to potassium, sodium or magnesium, important electrolyte minerals required for heart rhythm. IP6 does not remove calcium from bones or iron from red blood cells. Once chelated these excess minerals are excreted via the urinary tract. IP6 has been found to have similar iron-chelating properties as desferrioxamine, a drug commonly used to remove undesirable and excess iron from the body.	36,38
Curcumin	Turmeric	Curcumin induces increased genetic expression of the body's natural iron-binding and transport protein, ferritin further sequestering iron away from vulnerable tissues. These multiple capabilities lead directly to reduction in iron levels in iron-overloaded organs. Curcumin contributes to in vitro removal of non-transferrin bound iron by deferiprone and desferrioxamine in thalassaemic plasma.	43,44,45, 46,50
Lactoferrin, Silymarin and Silibinin	Milk	Lactoferrin, an effective iron chelator, binds to the Fe^{+} ions and decreases iron overload to the thalassaemic patients. Iron-overloaded animals can be protected from the liver fibrosis-inducing effects of iron by regular doses of silibinin, a milk thistle component**.**	53,54
Aestivum	Wheat grass	Triticum aestivum (wheat grass) is widely used in traditional medicine to treat various diseases. aestivum were established to have iron chelation potency and antioxidant activity.	57
Quercetin	Berries	Quercetin,which is a flavonoid found in berries and other plants, chelates iron atoms as powerfully as the prescription drugs used in managing severe cases of iron overdose. Its antioxidant effects are likely to be closely related to its strong iron-chelating capacity.	32,59,60, 61,62,63
Polyphenols	Cranberry and Pomegranate	Cranberry juice and extracts are active in preventing urinary tract infections with some of the most common pathological organisms, is a well-known fact. Cranberry extracts work is by depriving infecting bacteria of the iron they need for survival through chelation.	66,67
Epigallocatechin-3-gallate or EGCG	Green tea extracts	Green tea extracts rich in EGCG bind to iron, and scientists already proposed their use as an alternative or adjunct to commercial iron chelators, which, while effective, may come with negative side effects. EGCG from green tea has now been used safely and a well as effectively to bind and remove iron from the blood of individuals with thalassaemia.	73,74,75, 76

Conclusion:-

Iron chelating medicines as well as drugs are very costly to afford for poor peoples. In the same time if someone who could not take iron chelating drugs even after repeated blood transfusion, then excess of iron get stored in the body, which is not good for health. Thus those patients who are on regular blood transfusion can take the natural agents with high iron chelating potential to reduce their excess iron, stored in their body. Natural iron chelating agents may have the effective iron chelation potential. So, mainly our goal is to introduce natural agents which have iron chelating capability, instead to costly drugs. So, the poor patients can take the natural chelating agents and can avoid excess iron overload due to blood transfusion at much lower cost and without having bad side effects of the iron chelating drugs.

So, this paper will enlighten all concern people; clinicians, patients, health workers with natural agents as newer alternatives to costly iron chelating drugs with harmful side effects. Not only the natural agents will bring hope and promise to the patients who cannot afford cost iron chelating drugs, but also it attracts the pharmaceutical companies to promote research on these agents, extract active ingredients and formulate newer generation of iron chelating drugs at lower price and lesser side effects.

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