Traditional Alternatives in the Treatment of Iron Deficiency Anemia

Anupama Kalia, Monica Gulati*, Rajesh Kumar, Sachin Kumar Singh, Chander Mohan
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144402, India.

ABSTRACT

Imbalance of iron owing to lesser availability in diet, rapid growth of person and abnormalities associated with blood loss generally leads to Iron deficiency anemia. Anemia should not be ignored as it is related to adverse effects on general health. Anemic females and their neonates are at higher risk of death during the perinatal period. Milestones of mental and physical development among children are by anaemia. Even their physical work capacity and productivity may be reduced. Despite the easy and convenient diagnostic tests and availability of medicinal iron preparations, the condition is still quite prevalent. Various strategies including modern/traditional treatment have been used for curing IDA. While the modern treatment is associated with side effects like diarrhoea, indigestion, nausea, vomiting, constipation etc., the traditional Indian treatment is reported to be comparatively safer. Certain modified release haematinics have been designed to overcome the side effects associated with the conventional allopathic haematinics. However, such formulations are quite expensive. Many ayurvedic preparations containing iron are available in market. These include *Lauha bhasma* and *Mandoor bhasma*. Therapy with these is much safer and cost effective too. This paper summarizes the manifestations associated with iron deficiency anemia, various strategies of treatment and their possible outcomes.

Key Words:, *Iron Deficiency Anemia, haematinics, Ayurvedic, bhasma*

INTRODUCTION

Insufficient absorption of iron, decreased iron intake and loss of iron often from intestinal bleeding or menses are the commonest causes of Iron deficiency anemia (IDA). This state ultimately leads to reduction in the formation of hemoglobin, which contains iron. In India and other developing countries, IDA is a highly prevalent nutritional deficiency disorder. The age group most vulnerable to this disease is that of young children of both genders and women in their reproductive age group. Data indicates that 87% of pregnant females suffer from anemia with around 10% of them having severe anemia (Hb< 7 g/dl). The rate of prevalence of IDA varies within India with Andhra Pradesh having the minimum percentage as 33%, while Rajasthan shows highest prevalence of 98% [1]. High prevalence of IDA has been found in the children of slum areas, as a study in a slum area in Delhi indicated a prevalence of 76% [2]. On an average, a 68% prevalence rate has been reported in pre-school children [3]. It is considered as a serious problem of public health significance. A survey conducted by WHO for the year 1993-2005 revealed the global prevalence of IDA to be 1620 million [5].

ETIOLOGY OF IRON DEFICIENCY ANEMIA

Increased requirement of iron due to rapid growth owing to expanding cell mass and growing body tissue makes the adolescents more vulnerable to iron deficiency [6]. Rise in the volume of blood and muscle tissue mass escalates the need of iron in males, especially during puberty [7, 8]. However, in females, the iron requirement persists to be high after menarche, because of loss of about 20 mg of iron per month on average during menstruation but could go upto 58 mg in some women. Adolescents, particularly females, are known to have iron consumptions of 10-11 mg/day, leading to absorption of approximately 1 mg only [9]. Large percentages (75%) of adolescent women do not consume the stipulated dietary iron requirements while this percentage is only 17 for males [7]. In spite of reduction in the iron loss to nil due to menstruation during pregnancy, additional requirement of iron arises because of the embryo, placenta and increased maternal volume of blood. This increases the requirement of iron to 1000 mg over the entire pregnancy [10]. Iron need during the first trimester is relatively low i.e. 0.8 mg per day, but increases considerably during the next two trimesters to 6.3 mg per day. Part of this increased need is satisfied by the iron stores and by an adaptive increase in the absorption of iron. However, when the stored iron levels are less and dietary iron is poorly absorbed, its supplementation becomes mandatory. In lactating mothers, the absence of menstrual blood loss is compensated to some extent due to loss of iron approximately to the tune of 0.3 mg/day during lactation. A lactating mother's mean iron requirement during the first 6 months of lactation is about 1.3 mg/day [10]. In older individuals, the major reason behind iron deficiency may be chronic bleeding, cancer, diverticuli, or angiodysplasia [11]. Other reasons include reduced absorption [12]. It may develop as a co-morbidity of atrophic body gastritis [13]. The major factors leading to IDA are summarized in Fig. (1) [14, 15, 16].

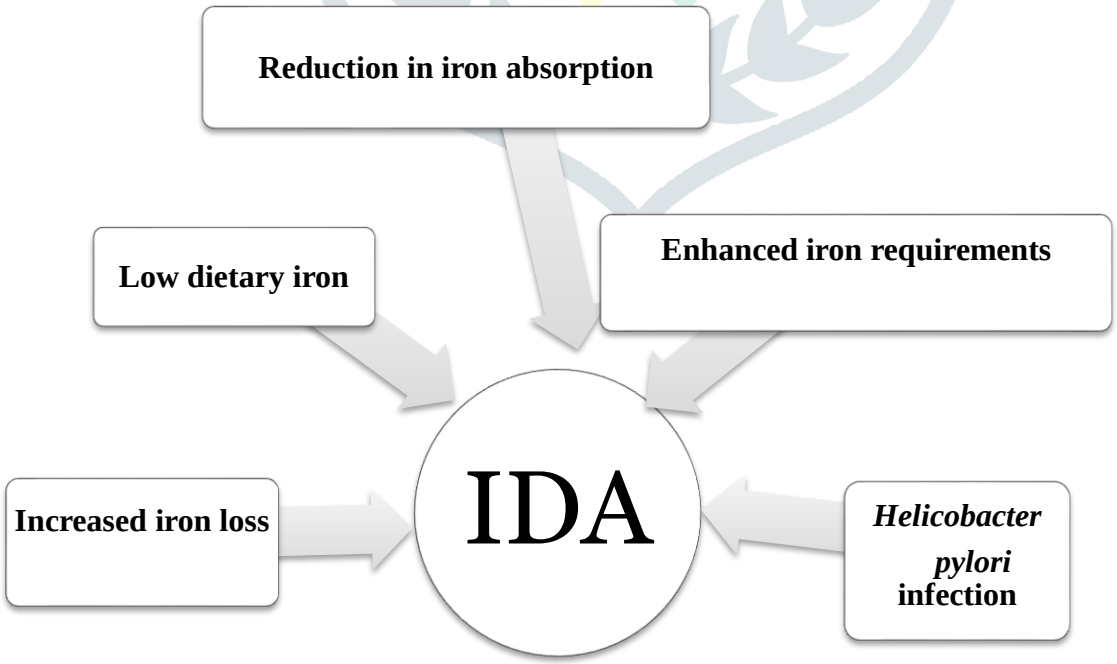

Fig. (1). Factors leading to Iron deficiency anemia

CONSEQUENCES OF IRON DEFICIENCY ANEMIA

Iron is the essential requirement of all the cells. All the major metabolic processes including metabolism, growth and differentiation of cells, gene regulation, oxygen binding and transport, use and storage of muscle oxygen, enzyme reactions, synthesis of neurotransmitters and proteins require iron [17]. Iron plays varied biological functions. Because of this, the impacts of its deficiency are wide-ranging. IDA generally remains unrecognized in the initial stages as it occurs slowly and takes time to develop the adaptation [18]. IDA constitutes one of the major risk factors in pregnancy. It is reported that more than 15% of maternal deaths are attributed to anemia [19]. Anemia, in mother, in turn, enhances prenatal mortality, low birth weight, and fetal wastage in addition to maternal immune depression and increased morbidity [20]. Pregnant women from low income strata in India with IDA have exhibited a three times higher incidence of premature deliveries as compared to their normal counter parts. It has been shown that IDA often leads to irreversible compromise in the learning ability of the children and exerts a negative influence on development of their mental abilities [21, 22]. This is attributed to disturbance in the formation of myelin tissue in the CNS [23,24]. Although, the neurochemical roles of iron are still unknown, socio-cultural and socio-economic factors along with compromised physical activity of these children should be studied [25]. However, it is very well documented that low levels of iron exert an adverse effect on neuron activity [26].

LABORATORY DIAGNOSIS OF IDA

The Centre for Disease Control and Prevention (CDC) has provided recommendation regarding screening of various age groups in context to anemia. The assessment of all the females is recommended to be done at least once every five years with respect to IDA, if other features of risk for anaemia are absent. In that case, the assessment becomes mandatory with immediate effect. On the contrary, adolescent males need to be assessed for anemia only if some risk factors are there [7]. Iron status is related to the erythropoiesis as well as the stored iron. In case of iron loss, stores are decreased while erythropoiesis is preserved. A single diagnostic test alone cannot specifically indicate IDA. A number of tests are required to be performed in the diagnosis anemia [27]. Various tests along with their advantages and limitations are tabulated in Table 1.

Table 1. Cut off points for the tests used in the diagnosis of anemia.

Gender/Age (yrs)	Hemoglobin (<g/dL)	Hematocrit (<%)
Children		
< 5	11.0	33.0
5-11	11.5	34.0
12-14	12.0	36.0

Females			
12-14.9	11.8	35.7	
15-17.9	12.0	35.9	
18+	12.0	35.9	
Pregnant woman	11.0	33.0	
Males			
12-14.9	12.5	37.3	
15-17.9	13.3	39.7	
18+	13.5	39.9	
Advantages	Inexpensive	Universally available	
Limitations	Low specificity	Low specificity	
Parameter	***Test Value***	***Advantages***	***Limitations***
Serum Ferritin	<15 µg/L	Quantitative Well standardized	Affected by inflammation & liver disease
Serum transferrin receptor concentration (TfR)	>8.5 mg/L	Quantitative Unaffected by Inflammation	Lacks standardizatio n
Transferrin saturation	<16%	Inexpensive, Well established	Wide diurnal variation Low specificity
Mean cell volume (MCV)	<82/85 fL*	Widely available	Late indicator
Red cell distribution width (RDW)	>14%	Early indicator	Limited availability
Erythrocyte protoporphyrin (FEP)	>70 µg/dL	Portable assay	Automation difficult
*** <15 yrs/>15 yrs of age**			
Severe anemia: Hemoglobin < 7g/dl			
Very severe anemia: Hemoglobin < 4g/dl			

TREATMENT STRATEGIES FOR IDA

The prevalence of IDA is still persistent in spite of the easy access of the diagnostic tests as well as haematinics. The choice of the treatment modality depends majorly upon the underlying cause, severity of disease; frequency for which treatment is to be given and the most important is the associated effects with the long-term treatment. The most common strategy is to overcome the iron deficiency through diet. Other medicinal treatment strategies include allopathic or ayurvedic treatment for curing IDA.

Dietary supplements

After the diagnosis and addressal of the root cause of IDA, the matter of concern is the restoration of the iron supply & iron stores in the body. On the basis of assumption that the mean rate of absorption of iron is 10% from the haematinics, the daily requirement of iron varies with the age group. In paediatric patients, adult males and women of postmenopausal age group, daily iron requirement is 10 mg (leading to availability of 1 mg). However, in young menstruating women and pregnant women, the iron requirement is 20 mg/day & 30 mg/day respectively. Further, the iron needs enhance in the patients with malabsorption of iron e.g. the patients who have had gastric bypass surgery done [28]. In case, the dietary history suggests a deficiency, foods rich in heme iron, such as meat, poultry and sea food are recommended to be administered by the patient [29]. Whole grains, nuts, legumes and green leafy vegetables contain non-heme iron, which is not much efficiently absorbed [30]. Ascorbic acid is also reported to enhance its absorption and co-administration of citrus fruits may help in enhancing the absorption further. However, in a study by Srigiridhar et al, an interesting observation was noted that when anaemic rats were fed with a mega dose of iron in combination with vitamins C and E, both of which exert strong anti-oxidant effect, most of the intestinal oxidative stress induced due to deficiency of iron get diminished. However, co-administration of only vitamin C was not found to be as effective. Rather, it was found to enhance the adverse effects of high doses of iron [31]. Therefore, it is advisable to administer the therapeutic dose of iron in combination with ascorbic acid and μ-tocopherol, in order to reduce the oxidative stress associated with IDA. Contrary to this, tea is reported to hinder its absorption. It is therefore, recommended to maintain a gap of 1 to 2 hrs between meals and tea [32]. Thus, a diet rich in vitamins is recommended in case of IDA. For a normal person, a diet containing 3.5-5.0 mg of vitamin E and 25-30 mg of vitamin C per 1000 Kcal is recommended. Food sources of tocopherol include wheat germ, wheat grain, almonds, peanuts, hazelnuts, and oils from vegetable sources like sunflower, safflower, soybean, wheat germ, and corn. Ascorbic acid is found sufficiently in fresh fruits [33]. Iron fortification of commonly used essential substances like common salt and wheat flour can also be one of the approaches to combat iron deficiency anemia [34]. Although nutrition review, assessment and counselling play an important role in the treatment, however, diet alone is usually not sufficient in most of the patients suffering from IDA [35].

Haematinics

Allopathic treatment

Iron supplementation can be done by oral as well as systemic route which includes intramuscular as well as intravenous route depending upon the severity of the disease. In extreme cases, blood transfusions may become necessary [36]. Iron supplements are available in almost every dosage form, which includes formulations containing ferrous sulfate, ferrous gluconate, ferrous fumarate, and extended-release carbonyl iron and iron-polysaccharide complex as the active ingredients. All the ferrous salts are equitably tolerated and effective in curing the deficiency [37]. Among these, ferrous sulfate is cost effective constitutes the first line therapy [37, 38]. Ferrous salts should be on fasting. Administration of 250 mg of ascorbic acid in combination with ferrous salts in order to increase the absorption is recommended. Other options include prolonged-release formulations [38, 39], liquids [40], iron salts with low elemental iron percentage, and taking the dose post prandially [41]. An intake of 200 to 300 mg/d of iron will lead to absorption of about 50 mg/d [7]. Parenteral route is often recommended to the patients having intolerance to the oral iron, those with severe GI bleeding and malabsorption syndrome [42]. Injectable formulation is available in the form of iron dextran, ferric gluconate, and iron sucrose. However, it may lead to anaphylaxis [43].

Risks associated with allopathic treatment

Although various allopathic iron preparations are helpful in the cure of iron deficiency anemia, many of these if used for longer time or in higher dose are associated with many risk factors. Most common side effects associated with oral iron therapy are heart burn, nausea, vomiting, stomach pain, blackening of stools and constipation. Iron supplements were found to generate free radicals which in turn are correlated with high risk of colorectal cancer [44]. In a report by Elizabeth et al, a group of eighteen healthy volunteers were selected, their food intakes were recorded and samples of their faecal matter before, during, and after 2 weeks of ferrous sulphate treatment were studied for total, free, and weakly chelated fecal iron. Significant increase in fecal iron was observed during the supplementation period, which, within 2 weeks, reverted back to the baseline. During supplementation, the concentration of weakly-bound iron in feces was found to increase substantially [45]. Iron supplements, if administered in higher doses may lead to development of disease in various ways. Excess of iron may have serious consequences like infection, neoplasia, cardiomyopathy, arthropathy, and a profusion of endocrine and possibly neurodegenerative disorders [46, 47, 48, 49]. Further, during infection and inflammation, and diseases related with ischemia and reperfusion, iron undergoes reactions leading to the production of superoxide radicals [50], which in turn reduces nonprotein bound ferric ions. The production of hydroxyl radicals may degrade polysaccharides, break DNA strands, deactivate enzymes, and stimulate lipid peroxidation [51]. Lozoff et al concluded in the study that extended oral therapy does not correct the lowered mental development associated with IDA [52].

In comparison to the oral therapy, the adverse effects of parenteral iron are readily occurring and more serious which include reactions at the site of injection such as pain, fever, muscle necrosis, phlebitis as well as

anaphylaxis, urticaria, and flare of rheumatoid arthritis. The delayed reactions include regional lymphadenitis, myalgia, arthralgia etc. Although, most of the reactions are mild and transient, the anaphylactic reactions may be serious [53].

Indian System of medicine- Ayurveda

Various ayurvedic preparations are available for the cure of iron deficiency anemia and to combat the side effects or adverse effects associated with allopathic supplements [54]. In Ayurveda, iron and other metals are administered in form of bhasma, which under predefined conditions, is prepared by heating raw material at elevated temperatures. The major steps involved in bhasma preparation include sodhana (purification), marana (detoxification) and bhasmikaran (process of making bioincompatible to bio-compatible). Sodhana is the purification process in which metal is dispersed into the herbal extract and repeated heating and cooling cycles were undergone. After shodana process, the material was ground using appropriate herbal juice for various days, depending upon the nature of the material, this process is known as marana. The process of marana leads to reduction in the particle size, thereby increasing the surface area for the quick abrsorption in the body. Marana process is followed by bhasmikaran in which the product obtained from shodhana/marana is repeatedly triturated with herbs (bhavana) and calcined in closed earthen pots in a pit, to obtain bhasma. The repetition of this procedure is done number of times as recommended in the classical literature for individual preparation depending upon the nature of metal. Although bhasmas are widely used in Ayurveda, however, till now the actual chemical change that occurs during the process is not clear. It is astonishing fact that in Ayurveda, processing of one metal with different sets of herbs yields the bhasma, which can be utilized for the treatment of different diseases. A study is needed to be carried out to understand the mechanism by which the consumption of metal present in bhasma takes place by the body to give desired medicinal effect [55]. Sarkar et al stated bhasmas to be the biologically produced nanoparticles [56]. Lauha bhasma & Mandoor bhasma are the classical Indian herbo-mineral products having incinerated iron and incinerated iron oxide respectively as one of their major ingredients. These are known to be the rejuvenators of the rakta dhatu (Blood) which is one of the seven essential factors that apprehend the very existence of the body and is said to be one of the ten abodes of the life mentioned in ayurvedic classics [57]. Along with this, the Indian medicine system, also provides a variety of iron preparations which are being used for centuries [58]. Various herbs when prescribed as formulations in combination with lauha bhasma or mandoor bhasma have been found to be the most effective remedy in the treatment of IDA along with the other associated ailments without any side effect associated with the allopathic treatment for the same [59]. Some of the important herbs associated with the treatment of IDA are summarized below.

Punarnava (*Boerhavia Diffusa*)

Punarnava is a part of many ayurvedic products in the market as Punarnava ambu, Punarnavaasav, Punarnava guggulu, Punarnava ghrit, Punarnava mandoor etc. Punarnava may also be given alone in swarasa form sometimes [60]. Its dose depends on the severity of the disease and the type of punarnava preparation

prescribed. However, the dose of Punarnava mandoor is 500 mg – 1 g once or twice a day [61]. It is the drug of choice in the treatment of various disorders of the liver such as iron deficiency anaemia, jaundice, hepatitis, anorexia, and sluggish liver. This herb has been reported to recondition the liver, purify the blood and aid in enhancing the haemoglobin level of patient [62].

Triphla

Triphala is an important *rasayana* drug, which is in used since ancient times. It has been described as a "tridoshic rasayana in the Ayurveda (Charka 1500 BC). It has balancing and rejuvenating effects on *vata*, *pitta*, and *kapha* (3 constitutional elements which govern human life) [63]. Triphla is composed of Amla *(Phyllanthus Emblica Linn)*, Bihara *(Terminalia Bellerica Gaertn.)* and Haritaki *(Terminalia Chebula Retz)* mixed in equal proportions. It is used as a very beneficial remedy in the treatment of iron deficiency anemia and used in the preparation of various ayurvedic formulations for the cure of associated ailments [64].

Guduchi *(Tinospora cordifolia*)

Guduchi is "the one who protects the body against diseases". As it promotes longevity, hence, it is known as Vayastha. It is most commonly used for the treatment of iron-deficit anemia in the form of *lauha kalpa* [65]. Along with this, it helps in increasing the effectiveness of leucocytes and in building the body's own defense mechanism (immune system) [66].

Shilajit

Shilajit is a wonder medicine of Ayurveda. It is neither a plant nor an animal substance, rather it's a mineral pitch which oozes from the Himalayan rocks, when they become hot in the summer season. It is said that Shilajit carries the healing power of mountains. Shilajit was described as a cure for all the disease by Caraka Samhita and Susruta Samhita. It is a rasayana (rejuvenative) which increases longevity from 100 to 1000 years of age. The extracts of shilajit and the humic compounds containing high level of iron are very useful remedy in the treatment of IDA [67]. Velmurugan ***et al*** evaluated the safety of shilajit by 91 days repeated administration in different dose levels in rats and concluded that black shilajit is safe for long term use as dietary supplement for a number of diseases and specifically IDA [68].

Reetha (*Sapindus Mukorossi*)

Commonly known as soapnuts, reetha powder has diversity of uses. Majorly saponins (10-11.5 %), sugars (10 %) and mucilages are present in fruits. The fruit has been reported to possess emetic, expectorant, alexipharmic, and abortificiant properties. Their saponins are known to have *in vitro* spermicidal activity which enables their use in contraceptive cream. The alcoholic Ritha extract (*Sapindus trifoliatus* Linn) has shown anti-implantation activity [69]. Along with this, Reetha fruits are very rich source of iron and often

used for the treatment of iron deficiency anemia, although much research has not yet been done to explore its use in the treatment of anemia [70].

As disussed, various natural herbs are known but need to be researched for use in the treatment of IDA. Sharma *et al* in a study compared the efficacy of ayurvedic preparations with allopathic preparations in the treatment of iron deficiency anemia and concluded that the ayurvedic preparations imparted a better response in comparison to the allopathic preparations and that to with lesser side effects. [71]. Various herbo-metallic preparations along with their composition used in the treatment of anemia are listed in Table 2.

Table 2. Commonly used herbo-metallic preparations used for the treatment of anemia

Name of the Drug	**Ingredients**	**Indications**	Ref
Punarnavadi *Maṇḍūra*	Punarnava, Trivrit, Trikatraya, Ushana, Pippalimula, Chavya, Chitraka, Devadaru, Pushkara, Katuki, Indrayava, Haridra, Darvi	Anaemia, Worm infestation, Inflammatio ns, Digestive diseases.	[72]
Triphaladi *Mandura*	Trikatraya, Chaturjata, Kalajaji, Ajamoda, Yashti, Dhanyaka	IDA	[72]
Thrayushanadi *Mandura*	Trikatraya, Chavya, Darvi, Dalchini, Pippalimula, Devadaru	IDA	[72]
Koladi *Mandura*	Chavya, Pippalimula, Shunti, Pippali	IDA	[72]
Navayasa *Lauha*	Amalakī, *Lauha bhasma* Yaṣti madhu, Amṛuta kvatha**,** Amalakī, Pippalī cūrṇa,	Anaemia, Dyspepsia, Duodenal ulcer	[73]
Saptamṛita *Lauha*	Yaṣtimadhu, Triphala, *Lauha bhasma*	Anaemia, Diseases of eye, Oedema	[74]
Shilajitvadi *Lauha*	Suddha Silajatu, Trikaṭu, Makṣika *bhasma*, *Lauha bhasma*	Anaemia	[65]
Tapyadi Lauha (without silver)	Triphala, Trikaṭu, Trimada, Suddha Silajīta, Svarṇamakṣika *bhasma*, *Lauha bhasma***,** Triphala,	Anaemia, Urinary disorders, Hepatic disorders, Oedema	[65]

Tapyadi Lauha (with silver)	Trikaṭu, Trimada, Suddha Silajīta, Svarṇamakṣika *bhasma, Lauha bhasma***,** Cīrayata,	Urinary disorders, Hepatic disorders, Anaemia, Oedema	[65]
Viṣama Jvarantaka Lauha	Pittapapḍa, Devdarū, Pṛiṣthaparṇī, Trikaṭu, Trayamaṇa, Giloya, Abhraka *bhasma*	Anaemia , Chronic fevers, Malabsorption syndrome.	[65]

Conclusion

In spite of accessibility of various types of iron formulations for treatment of iron deficiency anemia, the selection of a better preparation has always been felt. There are number of ayurvedic drugs which have been used for centuries for the cure of iron deficiency anemia, however, much scientific study on their efficacy as hematinic has not been carried out. Moreover, there are number of such formulations which are unavailable but suit the demand of present-day healthcare. This offers a scope for more researches on various formulations of iron and their indications. Ayurvedic medicinal system particularly considers the conditioning of mind and interaction with the environment which is evident from recommendation of specific life style to be followed while undergoing treatment. Hence, a need arises to undergo the research studies on such preparations used for the management of iron deficiency anaemia, thereby producing cost effective formulations without compromising the therapeutic effect.

References

1. Seshadri, S. In: *Malnutrition in South Asia: A regional profile*. Gillespie, S. Ed.; UNICEF Regional Office for South Asia, Kathmandu, **1997**, Vol. 5, pp. 75.
2. Gomber, S.; Kumar, S.; Russia, U.; Gupta, P.; Agarwal, K.N.; Sharma, S. Prevalence and etiology of nutritional anemia in early childhood in an urban slum. *Ind. J. Med. Res*., **1998**, 107, 269.
3. Damodaran, M.; Naidu, A.N.; Sharma, K.V.R. Anemia and morbidity in rural preschool children. *Ind. J. Med. Res*., **1979**, 69, 448.
4. Benoist, B.D.; McLean, E.; Egli, I.; Cogswell, M. Worldwide prevalence of anaemia 1993–2005. *WHO Global Database on Anaemia*. **2008**, 1-35.
5. Kwiatkowski, J.L.; West, T.B.; Heidary, N.; Whitley, K.S.; Alan R.; Cohen, M. Severe iron deficiency anemia in young children. *J. Pediatr*., **1999**, 135(4) 514-516.
6. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *Morb. Mortal. Wkly. Rep*., **1998**, 47, 1-29.

7. Wharton, B.A. Iron deficiency in children: detection and prevention. *Br. J. Haematol*., **1999**, 106, 270-280.
8. Beard, J.L. Iron biology in immune function, muscle metabolism and neuronal functioning. *J. Nutr*., **2001,** 131, 568S-579S.
9. Adenuga, W.; Ayinde, F.A. Nutrition for safer pregnancy, motherhood and infant survival. *Afr. J. Food Sci*., **2012**, 6(7), 186-203.
10. Guralnick, J.M.; Eisenstaedt, R.S.; Ferrucci, L.; Klein, H.G.; Woodman, R.C. Prevalence of anemia in persons 65 year and older in the United States: evidence for a high rate of unexplained anemia. *Blood*, **2004**, 104, 2063–2068.
11. Chaves, P.H.; Ashar, B.; Guralnik, J.M.; Fried, L.P. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? *J. Am. Geriatr. Soc.*, **2002,** 1527–64.
12. Nemeth, E.; Tuttle, M.S.; Powelson, J.; Vaughn, M.B.; Donovan, A.; Ward, D.M. Hepcidin regulates iron efflux by binding to ferroportin and inducing its internalization. *Sci.*, **2004,** 306(5704), 2090–2093.
13. Alleyne, M.; Horne, M.K.; Miller, J.L. Individualized treatment for iron deficiency anemia in adults. *Am. J. Med.*, **2008,** 121, 943-948.
14. Annibale, B.; Capurso, G.; Martino, G.; Grossi, C. Iron deficiency anemia and *Helicobacter pylori* infection. *Int. J. Antimicrob. Agents*, **2000**, 16, 515–519.
15. Cui, Y.; Wu, Q.; Zhou, Y. Iron-refractory iron deficiency anemia: new molecular mechanisms. *Kidney Int.*, **2009**. 76, 1137–1141.
16. Provan, D. Mechanisms and management of iron deficiency anemia. *Br. J. Haematol*., **1999,** 105(1) 19-26.
17. Barany, E.; Bergdahl, I.A.; Bratteby, L.E.; Lundh, T.; Samuelson, G.; Skerfving, S.; Oskarsson, A. Iron status influences trace element levels in human blood and serum. *Env. Res*., **2005,** 98, 215–223.
18. Kumari, P.; Kumari, N.; Ramalakshmi, B.A. Anemia and adverse obstetric outcome. *Nutr. Rep. Int.*, **1981**, 23, 637.
19. Kumari, P.; Ramalakshmi, B.A.; Madhavapeddi, R.; Babu, S. Immune status of anemic pregnant women. *Br. J. Obstet. Gynaecol.*, **1982,** 89, 222.
20. Grantham-McGregor, S.; Ani, C. A review of studies on the effect of iron deficiency on cognitive development in children. *J. Nutr*., **2001**, 131, 649S–668S.
21. Lozoff, B.; Jimenez, E.; Wolf, A.W. Long-term developmental outcome of infants with iron deficiency. *N. Engl. J. Med.*, **1991**, 325, 687–94.
22. Algarin, C.; Reirano, P.; Garrido, M.; Pizarro, F.; Lozoff, B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. *Pediatr. Res*., **2003**, 53, 217–23.

23. Connor, J.R,; Menzies, S.L. Relationship of iron to oligodendrocytes and myelination. *GLIA*, **1996**, 17, 83–93.
24. Idjradinata, P.; Watkins, W.E.; Politt, E. Adverse effects of iron supplementation on weight gain of iron-replete young children. *Lancet,* **1994**, 343, 1252–1254.
25. Seshadri, S.; Gopaldas, T. Impact of iron supplementation on cognitive functions in preschool children and school aged children: the Indian experience. *Am. J. Clin. Nutr.,* **1989,** 50, 675.
26. Cook, J.D. Diagnosis and management of iron-deficiency anaemia. *Best Pract. Res. Clin. Haematol.*, **2005,** 18(2), 319–332.
27. Kushner, R.F.; Retelny, S.V. Emergence of pica (ingestion of non-food substances) iron accompanying deficiency anemia after gastric bypass surgery. *Obes. Surg.*, **2005**, 15, 1491–1495.
28. Huang, X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. *Mutat Res*., **2003.** 533, 153–171.
29. Fly, A.D.; Czamecki-Maulden, G.L. Iron bioavailability from diets containing high-fibre breakfast cereals and crackers. *Nutr. Res*., **1996**, 16(2), 267-278.
30. Srigiridhar, K.; Nair, K.M. Supplementation with µ-tocopherol and ascorbic acid protects the gastrointestinal tract of iron deficient rats against iron induced oxidative damage during iron repletion. *Br. J. Nutr.*, **2000**, 84(2), 165–173.
31. South, P.K.; House, W.A.; Miller, D.D. Tea consumption does not affect iron absorption in rats unless tea and iron are consumed together. *Nutr. Res.*, **1997**, 17(8), 1303-1310.
32. Besarab, A., Coyne, D.W. Iron supplementation to treat anemia in patients with chronic kidney disease. *Nat. Rev. Nephrol.,* **2010**, 6, 699–710 .
33. Martınez-Navarrete, N.; Camacho, M.M.; Martınez-Lahuerta, J.; Martınez-Monzo, J.; Fito, P. Iron deficiency and iron fortified foods-a review. *Food Res. Int.*, **2002,** 35, 225–231.
34. Love, A.L., Billett, H.H. Obesity, bariatric surgery, and iron deficiency: true, true, true and related. *Am. J. Hematol*., **2008,** 83, 403-409.
35. Schrier, S.L. Treatment of anemia due to iron deficiency. http://www.uptodate.com/contents/treatment-of-anemia-due-to-iron-deficiency?source=search_result&search=Treatment+of+anemia+due+to+iron+ deficiency &selectedTitle=1~150 (Accessed September 4, **2012**).
36. Drugs information online. Iron preparations, oral. http://www.drugs.com/ monograph/ iron-preparations-oral.html (Accessed on September 4, **2012)**.
37. McDiarmid, T.; Johnson, E.D. Are any oral iron formulations better tolerated than ferrous sulfate? *J. Fam. Pract*., **2002**, 51, 576.

38. Adamson, J.W. In: Harrison's principles of internal medicine; Kasper, D.L.; Braunwald, E.; Fauci, A.S.; Hauser, S.L.; Longo, D.L., Jameson, J.L., Eds.; McGraw-Hill: New York, **2005,** 16th ed., pp. 586- 592.
39. Goddard, A.F.; McIntyre, A.S.; Scott, B.B. Guidelines for the management of iron deficiency anemia. *Gut*, **2000**, 46, 1-5.
40. Umbreit, J. Iron deficiency: a concise review. *Am. J. Hematol*., **2005,** 78, 225-231.
41. Auerbach, M.; Witt, D.; Toler, W. Clinical use of total dose intravenous infusion of iron dextran. *J. Lab. Clinic. Med*., **1988,** 111, 566-570.ici
42. Besarb, A.; Frinak, S.; Yee, J. An indistinct balance: the safety and efficacy of parenteral iron therapy. *J. Am. Soc. Nephrol*., **1999**, 10, 2029-2043.
43. Wurzemann, J.I.; Silver, A.; Schreinemachers, D.M.; Sandler, R.S.; Everson, R.B. Iron intake and risk of colon cancer. *Cancer Epidemiol. Biomark. Prev.*, **1996**, 5, 503–507.
44. Lund, E.K.; Wharf, S.G.; Fairweather-Tait, S.J.; Johnson, I.T. Oral ferrous sulfate supplements increase the free radical–generating capacity of feces from healthy volunteers. *Am. J. Clin. Nutr.*, **1999**, 69, 250–255.
45. Kontoghiorghes, G.J.; Weinberg, E.D. Iron: mammalian defense systems, mechanisms of disease, and chelation therapy approaches. *Blood Rev.*, **1995**, 9, 33-45.
46. Weinberg, E.D.; Weinberg, G.A. The role of iron in infection. *Curr. Opin. Infect. Dis*., **1995**, 8, 164-169.
47. Weinberg, E.D. The role of iron in cancer. *Eur. J. Cancer Prev*., **1996,** 5, 19-36.
48. Connor, J.R.; Beard, J.L. Dietary iron supplements in the elderly: to use or not to use? *Nutr. Today*, **1997**, 32, 102-9.
49. Tuomainen, T.P.; Punnonen, K.; Nyyssonen, K,; Salonen, J.T. Association between body iron stores and the risk of acute myocardial infarction in men. *Circulation*, **1998**, 97, 1461-1466.
50. McCord, J.M. Effects of positive iron status at a cellular level. *Nutr. Rev.*, **1996**, 54, 85-88.
51. Lozoff, B.; Wolf, A.W.; Jimenez, E. Iron-deficiency anemia and infant development: effects of extended oral therapy. *J. Pediatr*., **1996,** *129*(*3*), 382-389.
52. Kumpf, V.J.; Holland, E.G. Parenteral iron dextran therapy. *Drug Intell. Clin. Pharm. - The Annals of Pharmacotherapy*, **1990**, 24(2), 162-166.
53. Lauha & Mandur. http://www.umaayurvedics.com/lauha-*mandoor*.htm. (Accessed September 4, **2012)**
54. Raisuddin, S. In: *Scientific Basis for Ayurvedic Therapies; Mishra, L.C., Ed.;* CRC Press LLC: New York, 2004; pp. 84-90.
55. Sarkar, P.K.; Chaudhary, A.K. Ayurvedic *bhasma*: The most ancient application of nanomedicine. *J. Sci. Ind. Res*., **2010**, 69, 901-905.

56. Tripathi, A.; Joshi, B.; Singh, H.S.; Rathore, J.S.; Sharma, G. Chemical phases of some of the Ayurvedic heamatinic medicines. *Int. J. Eng. Sci. Technol.*, **2010**, 2(8), 25-32.
57. Nadkarni, K.M. *The Indian Materia Medica*, 3rd ed.; Popular Prakashan: Bombay, **1976**.
58. Shastri, R.D. *Bhaisajyaratnavali, Vidhyotini – Hindivyakhya - 'Vimarsh" - Parishishtasamhita*, 13th ed.; Chawkhambha Sanskrit Sansthan: Varanasi, **1997.**
59. Bhowmik, D.; Kumar, K.P. S.; Srivastava, S.; Paswan, S.; Dutta, A.S. Traditional Indian herbs punarnava and its medicinal importance. *J. Pharmacog. Phytochem.*, **2012,** 1(1) 59-65.
60. Ayurvedic Herbs as Healers - Punarnava and Ashwagandha. http://www.positivehealth.com/article /ayurvedic-herbs-as-healers-punarnava-and-ashwagandha (Accessed September 4, **2012**).
61. Ambika Das,[1] S Saritha, A clinical evaluation of Punarnavadi Mandura and Dadimadi Ghritha in management of pandu (Iron defeciency anaemia). Anc Sci Life. 2013 Jan; 32(Suppl 2): S86.
62. **Triphala Herbal Supplements.** http://www.herbalcureindia.com/triphala-trifala.htm (Accessed September 4, **2012**).
63. Jagetia, G.C.; Malagi, K.J.; Baliga, M.S.; Venkatesh, P.; Veruva, R.R. Triphala, an ayurvedic *Rasayana* drug, protects mice against radiation-induced lethality by free-radical scavenging. *J. Alt. Comp. Med.*, **2004**, 10(6), 971–978.
64. Gupta, K.L.V.; Pallavi, G.; Patgiri, B.J.; Prajapati, P.K. Critical review on the pharmaceutical vistas of *Lauha Kalpas* (Iron formulations). *J. Ayur. Integr. Med*., **2012,** 3(1), 21-28.
65. S. VEERAIAH AND K. JAGANMOHAN REDDY, CURRENT STRATEGIC APPROACHES IN ETHNOMEDICINAL PLANTS OF *TINOSPORA CORDIFOLIA* AND *GLORIOSA SUPERBA* – A REVIEW. International Journal of Pharma and Bio Sciences. Vol 3/Issue 2/April – June 2012.
66. David, F.; Vasant, L. *The Yoga of Herbs.* 2nd ed.; Lotus Press. Twin Lakes: WI, **2001**.
67. Velmurugan, C.; Vivek, B.; Wilson, E.; Bharathi, T.; Sundaram, T. Evaluation of safety profile of black shilajit after 91 days repeated administration in rats. *Asian Pac. J. Trop. Biomed*., **2012**, 210-214.
68. Francis, G.; Kerem, Z.; Makkar, H.P.S.; Becker, K. The biological action of saponins in animal systems: a review. *Bri. J. Nutr*., **2002**, 88, 587–605.
69. Soapnuts. http://www.soapnuts.co.uk/about_living_naturally.html (Accessed September 4, 2012).
70. Sharma, D.C.; Chandiramani, D.; Riyat, M.; Sharma, P. Scientific evaluation of some ayurvedic preparations for correction of iron deficiency and anemia. *Ind. J. Clin. Biochem.*, **2007**, 22 (2), 123-128.
71. Sen, G.D. *Bhaishajya Ratnavali*, 17th ed.; Chaukhamba Sanskrit Bhavan: Varanasi, **2004.**
72. Sandhya, P.; Grampurohit, N.D. Interaction of embelin and iron ayurvedic formlations. *Ind. J. Pharm. Sci*., 2004, 66, 739-744.
73. Sharma, K.R.; Bhatia, R.P.; Kumar, V. Role of the indigenous drug Sapthamrita Lauha in hemorrhagic retinopathies. *Ann. Ophthalmol*., **1992**, 24, 5-8.