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Efficacy of Oral Lactoferrin in Treatment of Iron Deficiency Anemia in Children admitted to Zagazig University Hospitals with Prolonged Chest Infection

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ORIGINAL ARTICLE

Efficacy of Oral Lactoferrin in Treatment of Iron Deficiency Anemia in Children admitted to Zagazig University Hospitals with Prolonged Chest Infection

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ABSTRACT

Background: It is a challenge to treat iron deficiency anemia in children with infectious conditions like pneumonia and empyema as using iron therapy with infection is controversial while blood transfusion is an unsafe alternative. Lactoferrin being a natural product of breast milk and its safe use in neonates and pregnant women may solve this dilemma.

Aim of the work: To evaluate efficacy of oral lactoferrin on hematological parameters and iron indices in children with iron deficiency anemia and prolonged chest infections.

Methods: We carried out an interventional study on 30 children aged between 6 months and 5 years admitted by prolonged chest infection requiring more than two weeks of therapy. Fifteen children received only the standard treatment of chest infection while the other 15 received 100 mg oral lactoferrin once daily plus the standard treatment. We excluded Children with chronic diseases other than chest diseases, children already on iron therapy and children who received packed RBCs or whole blood within the past 3 months. All included children were subjected to thorough history taking, vital signs recording and Laboratory investigations including CBC, CRP, Serum iron, Ferritin, TIBC and Transferrin saturation at baseline and 1 month after treatment.

Results: No statistically significant improvement in hematological parameters or iron indices was found between the two groups after one month of treatment.

Conclusion: Oral Lactoferrin failed to improve iron deficiency anemia with prolonged chest infections. It did not improve the microcytic hypochromic anemia present and showed an insignificant increase in iron indices.

Key words:
Lactoferrin, iron deficiency anemia, prolonged chest infection, hemoglobin, iron.

INTRODUCTION

Anemia is a condition in which the number of red blood cells is insufficient to meet the body's physiologic needs. Iron deficiency is the most common cause of anemia globally. Iron deficiency anemia (IDA) in children occurs most frequently between the age of 6 months and 5 years, the same period of age when repeated infections occur [1].

Using iron therapy for cases with IDA during time of infection caused a large debate about whether to give iron during that time or to wait until treatment of the infection, as there is no convincing data regarding its benefit or harm [2].

Lactoferrin (LF) is a glycoprotein found in significant concentrations in human colostrum and in lesser concentrations in human milk. It is a component of innate immunity and a

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potent immunomodulator [3]. Lactoferrin can be used to decrease late onset sepsis in neonates without adverse effects [4] and it can be used in treatment of iron deficiency anemia in pregnant females [5]. Oral administration of LF is effective in increasing hematological parameters by restoring iron homeostasis through direct or indirect modulation of hepcidin and ferroprotein (Fpn) synthesis [6].

It is a challenge to treat iron deficiency anemia in children with conditions like pneumonia, empyema or lung abscess as using iron therapy with infection is controversial [2] while blood transfusion is an unsafe alternative [7]. Lactoferrin, being a natural product of breast milk plus its safe use in neonates and pregnant females, encourages us to use it trying to solve this therapeutic dilemma [4, 5]. We aim here to evaluate the efficacy of oral LF on the hematological parameters and iron indices in cases of IDA and chest infections that need more than 2 weeks of treatment.

PATIENTS AND METHODS

We conducted this interventional study on thirty children, with both iron deficiency anemia and prolonged chest infection that needed more than 2 weeks of treatment, admitted to Chest Unit in the department of Pediatrics, Zagazig University Hospital, throughout the period from September 2018 to march 2019.

Written informed consent was obtained from all participants' parents and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

We enlisted 30 children.They were divided into 2 groups:

Group (A): 15 children that received the standard treatment of prolonged chest infection only with no iron supplementation. It included 10 males and 5 females with their ages ranging from 6 to 60 months. The standard therapy consists of a combination of two antibiotics given empirically to cover wide spectrum of bacteria until results of culture and sensitivity are available

Group (B): 15 children that received 100 mg of oral Lactoferrin in the form of sachets with the standard treatment of the prolonged chest infection. It included 9 males and 6 females with their ages ranging from 9 to 60 months.

We excluded Children with chronic diseases other than chest diseases i.e. (with chronic renal, hepatic, cardiac, immunologic diseases or with malignancy), children already on iron therapy and children who received packed RBCs or whole blood within the past 3 months.

All children included in the study were subjected to thorough history taking including: Age, sex, duration of illness and history of previous iron therapy or blood transfusion. Vital signs including core body temperature and respiratory rate were obtained. Laboratory investigations were done including: CBC, CRP, Serum iron, Ferritin, TIBC and Transferrin saturation

The follow up of cases was done after 1 month, checking the vital signs (Core body temperature and respiratory rate) and repeating the laboratory investigations done at the start (CBC, CRP, Serum iron, Ferritin, TIBC and Transferrin saturation) and checking the effectiveness of oral Lactoferrin on improving the haematological parameters and iron indices.

Statistical analysis:

Results are considered significant if *P*-value < 0.05 and are considered insignificant if *P*-value > 0.05. All statistical analyses were performed using IBM SPSS Statistics, version 24 (IBM; Armonk, New York, USA).

RESULTS

Regarding to the characteristics of the studied children, there was no statistically significant difference in age (*P*= 0.20), sex distribution (*P*= 0.71) or type of pulmonary infections (*P*= 0.14) between group A and group B. (Table 1 is here)

In addition, there was no statistically significant difference in the baseline clinical findings (respiratory rate and core body temperature) between group A and group B (*P*= 0.72 and 0.35 respectively). (Table 2 is here)

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Baseline results:

There was no statistically significant difference in CBC and CRP between group A and group B (*P*> 0.05).

Group A had statistically significant higher baseline serum iron (*P*= 0.008) and Transferrin saturation (*P*= 0.015) than group B. Other serum iron indices were not significantly different between the two groups (*P*> 0.05). (Table 3 is here)

Results after the one month of follow up:

Both group A and group B had no statistically significant difference in hemoglobin, hematocrit, MCV and MCH compared with their levels before therapy.

Group A had statistically significant lower WBCs (*P*= 0.024), lower C-reactive protein (*P*= 0.001) and lower serum ferritin level (*P* = 0.001) compared with their levels before therapy. Other serum iron indices did not differ significantly at baseline and one month following standard therapy (*P*> 0.05). (Table 4 is here)

Group B had statistically significant lower WBCs (*P*= 0.001), lower C-reactive protein (*P*= 0.001), higher serum iron (*P* = 0.003), higher total iron binding capacity (*P*= 0.001) and significantly lower serum ferritin level (*P*= 0.006) compared with their levels before therapy. Transferrin saturation did not differ significantly (*P*= *0*.19) between baseline and one month following oral lactoferrin therapy. (Table 5 is here)

Group B had statistically significant higher total iron binding capacity than group A (*P*= 0.017). Other serum iron indices were not significantly different between the two groups (*P*> 0.05). (Table 6 is here)

Table 1: Demographic data of group A and B:

Characteristic	Group A	Group B	Test of significance	*P*-value
	Standard therapy only	**Oral Lactoferrin + standard therapy**		
	n=15	*n*=15		
Age (months)				
median(range)	18(6-60)	24(9-60)	81.5#	0.20
Sex, *n* (%)				
Male	10(67)	9(60)	x^2=0.14	0.71
Female	5(33)	6(40)		
Pulmonary infections, *n* (%)				
Prolonged pneumonia	10(67)	6(40)	x^2=2.1	0.14
Empyema	5(33)	9(60)		

x^2=Chi-squared test, # = Mann-Whitney *U* test, standard therapy= double antibiotics and antipyretics

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Table 2: Baseline clinical findings in group A and B

Clinical findings	Group A	Group B	Test of significance (Independent samples t-test)	*P*-value
	Standard therapy only	**Oral Lactoferrin +standard therapy**		
	n=15	*n*=15		
Respiratory rate (cycle/min)				
mean±SD	40±5	38±9	0.37	0.72
Temperature (^{0}C)				
mean±SD	38.6±0.6	38.7±0.4	0.95	0.35

Standard therapy= double antibiotics and antipyretics

Table 3: Baseline CBC, CRP and iron indices between group A and group B

Laboratory findings	Group A	Group B	Test of significance	P-value
	Standard therapy only	**Oral Lactoferrin + standard therapy**		
	n=15	**n=15**		
Haemoglobin (g/dL)				
mean±SD	9.3±0.92	9.7±0.98	0.9#	0.38
Hematocrit (%)				
mean±SD	28.5±3	29.8±3.2	1.2#	0.24
MCV (fl)				
mean±SD	66.9±5.5	65±8.6	0.6#	0.55
MCH (pg)				
mean±SD	20.9±2.6	21.3±2.8	0.4#	0.69
WBC ($\times10^3/\mu L$)				
median(range)	11.9(4.1-28)	19(4.9-36.7)	66#	0.056
C-reactive protein (mg/L)				
median(range)	72(21-250)	103(16-469)	69*	0.07
Serum iron indices				
Iron (µg/dL)				
mean±SD	34.6±8.9	25.4±9	2.8#	**0.008**
Total iron binding capacity (µg/dL)				
mean±SD	284.1±54.2	263±9	0.9#	0.40

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Ferritin (ng/mL)				
median(range)	150(27-485)	208(11-491)	111*	0.97
Transferrin saturation (%)				
mean±SD	12.3±1.8	9.9±3	2.6#	**0.015**

MCV= Mean corpuscular volume, MCH= Mean cell hemoglobin, WBC= white blood cell count, # = independant samples- t test, *= Mann-Whitney U test, standard therapy= double antibiotics and antipyretics

Table 4: CBC, CRP and iron indices one month following standard therapy in Group A

Laboratory findings	Group A		Test of significance	P-value
	Baseline	**After**		
	n=15	**n=15**		
Haemoglobin (g/dL)				
mean±SD	9.3±0.92	9.4±1.09	0.04#	0.97
Hematocrit (%)				
mean±SD	28.5±3	28.9±3.4	0.5#	0.64
MCV (fl)				
mean±SD	66.9±5.5	67±5.1	0.05#	0.96
MCH (pg)				
mean±SD	20.9±2.6	20.8±2.2	0.17#	0.87
WBC ($\times 10^3/\mu L$)				
mean±SD	13.4±6.5	9.1±2.9	2.5#	**0.024**
C-reactive protein (mg/L)				
median(range)	72(21-250)	3.7(0.2-31)	3.4*	**0.001**
Serum iron indices				
Iron (µg/dL)				
mean±SD	34.6±8.9	39.4±11.3	1.6#	0.13
Total iron binding capacity (µg/dL)				
mean±SD	284.1±54.2	301.3±42.1	1.2#	0.24
Ferritin (ng/mL)				
median(range)	150(27-485)	46.5(10.8-309)	3.2*	**0.001**
Transferrin saturation (%)				
mean±SD	12.3±1.8	13±3.2	1.2#	0.25

MCV= Mean corpuscular volume, MCH= Mean cell hemoglobin, # = Paired samples- t test, *= Wilcoxon Signed Ranks Test, standard therapy= double antibiotics and antipyretics

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Table 5: CBC, CRP and iron indices one month following oral lactoferrin therapy in Group B

Laboratory findings	Group B		Test of significance	*P*-value
	Baseline	**After**		
	***n*=15**	***n*=15**		
Haemoglobin (g/dL)				
mean±SD	9.7±0.98	9.8±1.02	0.3#	0.77
Hematocrit (%)				
mean±SD	29.8±3.2	29.9±2.7	0.09#	0.93
MCV (fl)				
mean±SD	65.4±8.6	67.4±7.8	1.5#	0.14
MCH (pg)				
mean±SD	21.3±2.8	21.2±2.6	0.34#	0.74
WBC ($\times 10^3/\mu L$)				
mean±SD	19.2±8.7	9.1±2.7	4.1#	**0.001**
C-reactive protein (mg/L)				
median(range)	103(16-469)	3.3(0.20-78)	3.4*	**0.001**
Serum iron indices				
Iron (µg/dL)				
mean±SD	25.4±9	36.4±11	3.6#	**0.003**
Total iron binding capacity (µg/dL)				
mean±SD	263.07±9.0	355.3±68.7	4.3#	**0.001**
Ferritin (ng/mL)				
median(range)	208(11-491)	45(13-148)	2.8*	**0.006**
Transferrin saturation (%)				
mean±SD	9.9±3	10.8±4.4	1.4*	0.19

MCV= Mean corpuscular volume, MCH= Mean cell hemoglobin, # = Paired samples- t test, *= Wilcoxon Signed Ranks Test.

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Table 6: Serum iron indices one month following therapy between the two groups

Serum iron indices	Group A	Group B	Test of significance	*P*-value
	Standard therapy only	**Oral Lactoferrin + standard therapy**		
	n=15	*n*=15		
Iron (µg/dL)				
mean±SD	39.4±11.3	36.4±11	0.7#	0.47
Total iron binding capacity (µg/dL)				
mean±SD	301.3±42.1	355.3±68.7	2.5#	**0.017**
Ferritin (ng/mL)				
median(range)	46.5(10.8-309)	45(13-148)	90.5*	0.37
Transferrin saturation (%)				
mean±SD	13±3.2	10.8±4.4	1.6#	0.11

= Independent samples t-test, *= Mann-Whitney *U* test, standard therapy= double antibiotics and antipyretics

DISCUSSION

In this original work, we studied for the first time the use of lactoferrin (LF) in children suffering from both lower respiratory tract infections (LRTIs) and iron deficiency anemia (IDA) in an attempt to improve iron homeostasis and at the same time to avoid giving iron therapy at the time of infection.

We followed our patients for 1 month after the LF treatment. This duration was considered in previous studies done on the lactoferrin effect on IDA in pregnant women as shown in the study of Abu hashim et al in 2017, where his systematic review and meta-analysis was conducted on four clinical trials showing the follow up period to be 1 month after the oral lactoferrin treatment [8]. We used the single dose of 100 mg oral lactoferrin based on the studies done for prevention of NEC in preterm neonates [9, 10].

There were no significant differences between our two groups regarding age, sex, type or severity of pulmonary infections denoting that children in both groups were matched and had similar demographic and clinical data.

There were no significant difference between baseline CBC and CRP between our two groups. However, regarding baseline serum iron indices, group B that received oral lactoferrin had statistically significant lower baseline serum iron and transferrin saturation than group A. The Other baseline serum iron indices were not significantly different in both groups.

In spite of the statistical difference in iron indices values, we considered that our two groups were clinically matched. In IDA, serum iron levels are below 40 µg/dL [11], so having serum iron of 25 µg/dL in group B or 35 µg/dL in group A did not differ much in the practical point of view and both are considered as having IDA. The same with transferrin saturation results as both 10% and 12% are in the same degree of ID with no difference in practice between those two results [11].

After the 1 month of LF treatment, there was no statistically significant improvement regarding the hematological parameters like hemoglobin, hematocrit, MCV and MCH. The effect of lactoferrin to improve the

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microcytic hypochromic anemia was not evident in our results.

This may be explained by the dose of LF given. While we used 100 mg of oral LF once daily, other studies used higher doses of oral LF. The pregnant women in the study of Rateb et al. used LF 100 mg twice daily [12] and the pregnant women in the study of Rezk et al. used 250 mg tablets of LF once daily [13].

We based our 100 mg oral dose on the studies done on neonates in cases of necrotizing enterocolitis (NEC) being the nearest age group to our study cases (6 months to 5 years) and being in a severe critical condition similar to our cases with prolonged chest infections [3, 9, 14].

As our results did not show the desired response on hematological parameters, using double this dose may be the key to solve this issue. Studies conducted on pregnant women suffering from IDA recommend using double this dose during treatment reaching 200 mg oral lactoferrin daily either once or 100 mg twice per day [15, 16].

We also used the duration of 1 month of follow up based on neonatal studies in which LF was used [9, 17]. In addition, this is mostly the duration that the cases of prolonged chest infection spent in our hospital and we wanted to improve their hematological parameters while in hospital receiving treatment and follow up their clinical progress.

Our results found a statistically significant increase in serum iron and total iron binding capacity in group B receiving oral lactoferrin with the standard therapy compared with their baseline levels. This was not found in group A receiving only our standard therapy. This is a statistical increase, practically speaking, the increase of serum iron in group B is insignificant and the child is still having IDA, and this is why instead of TIBC going down as sign of IDA resolving, it went up, showing that the body is still deficient in iron.

Both groups had a statistically significant lower serum ferritin level after 1 month of treatment compared with their baseline levels. This can be explained by the effect of the standard therapy on the present infection considering that ferritin is an acute phase reactant, which was expected to decrease with the resolution of the inflammation and infection [11]. This is probably why the decrease in serum ferritin levels was significant in both groups and was associated with significant reduction in WBCs and CRP in both groups after the 1 month of treatment.

However, when the effect of one month oral lactoferrin therapy (group B) on iron indices (iron serum level, TIBC, ferritin and TSAT) was compared to the standard therapy alone (group A), it failed to show statistically significant difference. It only had statistically significant higher total iron binding capacity than group A proving the failure of LF to treat IDA in such cases. Oral lactoferrin failed to show the promising effect that was expected in these cases. It did not improve the microcytic hypochromic anemia and the statistically significant increase of iron indices in group B after treatment was not significant when compared to the other group.

We previously explained that the reason may lie in the dose of LF given or the duration of LF intake. However, mode of administration may also affect the results. Lactoferrin is generally a protein compound, so it is subjected to enzymatic degradation in the GI tract, poor permeability across the intestinal epithelium and rapid clearance after being absorbed [18]. The stomach is the first enzymatic barrier that faces LF. It contains acid and pepsin that can degrade oral LF rendering it ineffective in treatment of ID and IDA [19]. The small intestine is the second enzymatic barrier against LF. It is further degraded to amino acids by the different intestinal proteolytic enzymes such as protease, trypsin and chymotrypsin [20].

In order to achieve the best effect of LF and overcome its enzymatic degradation and membrane permeation problems, many different delivery approaches are being developed which includes PEGylation, absorption enhancers and advanced drug carrier systems.

PEGylation is the attachment of polyethylene glycol (PEG) to therapeutic polypeptides, and it is found to improve both the pharmacokinetic and pharmacodynamic properties [21]. Absorption enhancers are chemical moieties that increase the permeability or transport of molecules across

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different biological membrane barriers. They act through different mechanisms of action such as a change in membrane fluidity, leakage of proteins through membranes, a decrease in mucus viscosity and opening tight junctions [22]. Nano-particulate carrier systems (<1 μm) such as microemulsions, liposomes and polymeric or lipid nanoparticles may improve the oral delivery of LF due to their intracellular endocytosis [23].

Regarding the limitations of our study, first of all, our study was the first to evaluate the effectiveness of oral LF in this age group (6 months to 5 years) and in this state of infection (prolonged chest infections), so we based our theory on the findings present in pregnant women and in neonates who suffered from NEC. There were no similar studies to compare our results to either positively or negatively.

The second limitation was the small number of cases (15) and controls (15), although it gave us a general idea about what to expect later on, is not enough to draw final definitive conclusions. Increasing sample size in the following studies will provide more power to the studies and provide us with stronger conclusions.

CONCLUSION

Oral Lactoferrin did not show the expected effect in improving IDA with prolonged chest infections. It did not improve the microcytic hypochromic anemia present and although it showed an increase in iron indices, it was not significant enough compared to the other group that did not receive lactoferrin.

Disclosure of potential conflicts of interest

The authors report no conflicts of interest.

REFERENCES

1. Avhad Y, Wade P, Ghildiyal RG. Anemia as a risk factor for lower respiratory tract infections (LRTI) in children. International Journal of Contemporary Medical Research. 2016; 3 (12): 3512-14.
2. Daoud E, Nakhla E, Sharma R. Q: Is iron therapy for anemia harmful in the setting of infection? Cleveland Clinic journal of medicine. 2011; 78 (3): 168-170.
3. Barrington KJ, Assaad MA, Janvier A. The Lacuna Trial: a double-blind randomized controlled pilot trial of lactoferrin supplementation in the very preterm infant. Journal of perinatology. 2016; 36 (8): 666-9.
4. Pammi M, Suresh G. Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. The Cochrane database of systematic reviews. 2017; 6.
5. Paesano R, Berlutti F, Pietropaoli M, Pantanella F, Pacifici E, Goolsbee W, et al. Lactoferrin efficacy versus ferrous sulfate in curing iron deficiency and iron deficiency anemia in pregnant women. Biometals. 2010; 23 (3): 411-17.
6. Paesano R, Natalizi T, Berlutti F, Valenti P. Body iron delocalization: the serious drawback in iron disorders in both developing and developed countries. Pathogens and global health. 2012; 106 (4): 200-16.
7. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Critical care medicine. 2008; 36 (9): 2667-74.
8. Abu Hashim H, Foda O, Ghayaty E. Lactoferrin or ferrous salts for iron deficiency anemia in pregnancy: A meta-analysis of randomized trials. European journal of obstetrics, gynecology, and reproductive biology. 2017; 219: 45-52.
9. Manzoni P, Meyer M, Stolfi I, Rinaldi M, Cattani S, Pugni L, et al. Bovine lactoferrin supplementation for prevention of necrotizing enterocolitis in very-low-birth-weight neonates: a randomized clinical trial. Early Human Development. 2014; 90: S60-S65.
10. Meyer MP, Alexander T. Reduction in necrotizing enterocolitis and improved outcomes in preterm infants following routine supplementation with Lactobacillus GG in combination with bovine lactoferrin. Journal of neonatal-perinatal medicine. 2017; 10 (3): 249-55.
11. Wu AC, Lesperance L, Bernstein H. Screening for iron deficiency. Pediatrics in Review. 2002; 23 (5): 171-7.
12. Rateb AM, Mamdouh AM, Balsha KM. The Effect of Orally Administered Iron-Saturated Lactoferrin on Systemic Iron Homeostasis in Pregnant Women Suffering from Iron Deficiency and Iron Deficiency Anaemia. Egyptian Journal of Hospital Medicine. 2018; 71 (4): 2851-7.
13. Rezk M, Dawood R, Abo-Elnasr M, Al Halaby A, Marawan H. Lactoferrin versus ferrous sulphate for the treatment of iron deficiency anemia during pregnancy: a randomized clinical trial. The journal of maternal-fetal & neonatal medicine. 2016; 29 (9): 1387-90.
14. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, et al. Bovine

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lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. Jama. 2009; 302 (13): 1421-8.
15. Lepanto MS, Rosa L, Cutone A, Conte MP, Paesano R, Valenti P. Efficacy of Lactoferrin Oral Administration in the Treatment of Anemia and Anemia of Inflammation in Pregnant and Non-pregnant Women: An Interventional Study. Frontiers in immunology. 2018; 9: 2123.
16. Paesano R, Torcia F, Berlutti F, Pacifici E, Ebano V, Moscarini M, et al. Oral administration of lactoferrin increases hemoglobin and total serum iron in pregnant women. Biochemistry and cell biology. 2006; 84 (3): 377-80.
17. Paesano R, Pacifici E, Benedetti S, Berlutti F, Frioni A, Polimeni A, et al. Safety and efficacy of lactoferrin versus ferrous sulphate in curing iron deficiency and iron deficiency anaemia in hereditary thrombophilia pregnant women: an interventional study. Biometals. 2014; 27 (5): 999-1006.
18. Yao X, Bunt C, Cornish J, Quek S-Y, Wen J. Oral Delivery of Lactoferrin: A Review. International Journal of Peptide Research and Therapeutics. 2012; 19 (2): 125-34.
19. Smart AL, Gaisford S, Basit AW. Oral peptide and protein delivery: intestinal obstacles and commercial prospects. Expert opinion on drug delivery. 2014; 11 (8): 1323-35.
20. Troost FJ, Saris WH, Brummer RJM. Orally ingested human lactoferrin is digested and secreted in the upper gastrointestinal tract in vivo in women with ileostomies. The Journal of nutrition. 2002; 132 (9): 2597-600.
21. Roberts MJ, Bentley MD, Harris JM. Chemistry for peptide and protein PEGylation. Advanced drug delivery reviews. 2002; 64: 116-27.
22. Mahato RI, Narang AS, Thoma L, Miller DD. Emerging Trends in Oral Delivery of Peptide and Protein Drugs. Critical Reviews in Therapeutic Drug Carrier Systems. 2003; 20 (2-3): 153-214.
23. Russell-Jones GJ. The potential use of receptor-mediated endocytosis for oral drug delivery. Advanced drug delivery reviews. 1996; 20 (1): 83-97.

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