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Supplementation of Ginger with Anti-Tuberculosis Treatment (ATT): A better Approach to Treat Anemic Pulmonary Tuberculosis Patients

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ABSTRACT

Anemia is seen in pulmonary tuberculosis patients and is associated with deregulation of iron metabolism due to alteration in Acute Phase Proteins mainly C-Reactive Proteins (CRP). Since ginger helps in the regulation of iron metabolism by decreasing CRP. So the present study is designed to assess the effect of ginger supplementation in anemic pulmonary tuberculosis patients. The study was carried out in 68 subjects of newly diagnosed sputum positive anemic Pulmonary Tuberculosis patients, falling in DOTS (CAT I) and 35 were healthy control subjects between 20-58 yrs of age. Study group were divided into two groups – One group were given ATT with ginger supplement and the another group ATT only for 30 days. In both groups, serum samples were analyzed for Hemoglobin (Hb), C - reactive protein (CRP), Ferritin, Serum Iron and Total Iron Binding Capacity (TIBC) on day zero (D-0) and 30th days of ginger supplementation. The ginger supplementation to anemic TB Patients led to significant decrease in CRP, Ferritin and significant increase in serum iron, Total Iron Binding Capacity which resulted into correction of anemia.

Keywords: Anemic pulmonary tuberculosis patients, Ginger supplementation, Acute phase Protein (CRP), Anti-tuberculosis treatment (ATT), Anti-inflammatory action.

1. Introduction

Tuberculosis (TB) remains one of the world's leading infectious causes of death among adults occurring predominantly in socio-economically deprived populations.One third of the world's population is thought to be infected with *M. tuberculosis* [1]. It is a chronic infectious disease, so anemia of inflammation may contribute significantly [2]. Acute Phase Proteins (APPs) are a class of diverse proteins whose blood plasma concentrations increase or decrease during the response to inflammation, in the acute phase [3]. The Precise mechanism of anemia in pulmonary tuberculosis is not known but anemia of inflammation as well as of iron deficiency could be responsible for this.[4]Iron and its homeostasis is intimately tied to the inflammatory response. In PTB patients alteration of Acute Phase protein (mainly C- Reactive Protein) leads to disturbance in iron metabolism. Since Anemia of chronic disease is multifactorial in origin [5], the only effective treatment for anemia of inflammation is correction of the underlying disorder [6].

Recent years have seen an increased enthusiasm in treating various diseases with natural products [7]. Ginger, as an antimicrobial [8], antioxidant [9], Anti-inflammatory and immunomodulatory agent [10] might prove to be effective supplement in the treatment of tuberculosis. Global trend in resistance to anti-tuberculosis drug was observed [11]. WHO has also recommended using the herbal drugs with anti-tubercular activities may also be used along with Anti-tubercular drug.The Present study was designed to know the therapeutic effects of ginger extract with ATT in newly diagnosed sputum AFB positive Pulmonary Tuberculosis patients having significant anemia and falling in DOT (CAT I).

2. Materials and Methods

Patients were selected from the Out Patient Department (OPD) of Medicine in SAIMS Medical College, Manorma Raje Tuberculosis Hospital and from different DOTS Centers of Indore (M.P).The subjects of this study consisted of 68 newly diagnosed sputum AFB positive Pulmonary Tuberculosis patients having significant anemia, falling in DOTS (CAT I) and 35 were healthy control subjects between 20-58 yrs of age. Anemic Patients were selected as per **WHO criteria** (for Male < 13gm/dL & for Female < 12gm/dL) [12]. Prior to start of study Informed consent was taken from each subject, and then they were enrolled in the study. The Ethical Committee (Institutional & Human) of SAIMS Medical College, Indore approved the study.

2.1 Ginger Supplementation: Powder ginger extract was obtained fromAmsar Laboratories Limited, Indore. One kilogram of solvent free ginger extract was prepared from six kilogram of raw ginger powder by solvent extraction method. One gram ofsolvent-free extract was equivalent to 6 gramof the dried ginger (W/W) powder. **Dose:** 250mg. of ginger extract (equivalent to 1.5gm of pure ginger powder) was given orally twice daily after meals for 30 Days in capsular form.

2.2 Study Design: DOTS patients were divided into two groups on the basis of ginger supplementation irrespective of age and sex. One group (GR- A) took the ginger supplement with ATT (n = 36) and the other group (GR- B) received standard ATT without the ginger supplement (n = 32). Both groups received standard ATT treatment.

2.3 Sample Collection & Method Applied: In the study group first batch of the blood samples were collected on day zero **(0-D)** before ginger supplementation and 2nd batch of sample was collected on thirtieth day **(D -30)** of ginger supplementation. Serum was obtained after centrifugewere stored in the appendrof tube at- **20 ºC**. Prior to use, the samples were allow to come at room temperature (22-28ºC) and mix by gentle inversion or swirling. Grossly hemolyzed and lipemic samples were excluded. All the samples were analyzed for: analyzed for: hemoglobin by automated cell counter (Sysmex KX-21), Serum C- reactive protein (by solid phase immunoenzymatic by using kit acquired from USA), serum ferritin by the method of Ronald H et al. [13], Serum iron by the method of Siedel J. et al. [14] and Serum Total Iron Binding Capacity (TIBC) by the method of Tietz NW [15].

2.4 Statistical Analysis: Paired and Unpaired t- test were used for statistical assessments with SPSS Version 10 to evaluate mean levels of variables in study groups. Values were expressed as Mean ± SD.

3. Results:

Table 1: Comparison of Parameters between control group and study group (Anemic Pulmonary Tuberculosis Patients)

Hb (g/dL)	14.46 ± 1.61	11.25 ± 1.12	9.742	< 0.001
CRP (µg/mL)	2.95 ± 0.72	37.99 ± 7.21	28.58	< 0.001
Ferritin (ng/mL)	161.31 ± 40.2	385.58 ± 80.08	14.84	< 0.001
Serum Iron (µmol/L)	18.97 ± 2.65	5.16 ± 2.47	22.67	< 0.001
TIBC (µg/dL)	306.34 ± 42.4	192.19 ± 46.05	10.84	< 0.001

Value are in Mean ± SD highly significant p < 0.001 **DF = 69**

The mean hemoglobin (Hb), Serum iron and TIBC levels in study group were lower and found to be highly significant (p < 0.001) as compared to control**.** A highly significant rise (p < 0.001) was noted in mean serum levels of C-reactive proteins and ferritin in study group as compared to control (**Table 1)**.

Table 2: Pre (Day Zero) and Post (30th Day) analysis of Biochemical Parameters in Anemic Pulmonary Tuberculosis Patients (ATT with Ginger Supplementation)

Parameter	Pre (0 Day)	Post (30th Day) (n =36)	t-test	p-value
Hb (g/dL)	11.25 ± 1.12	11.88 ± 1.21	13.04	< 0.001
CRP (µg/mL)	37.99 ± 7.21	20.67 ± 5.15	16.86	< 0.001
Ferritin (ng/mL)	385.58 ± 80.08	301.63 ± 70.13	8.59	< 0.001
Serum Iron (µmol/L)	5.16 ± 2.47	6.88 ± 2.43	14.73	< 0.001
TIBC (µg/dL)	192.19 ± 46.05	295.94 ± 51.85	16.10	< 0.001

Table 3: Pre (Day Zero) and Post (30th D) analysis of Biochemical Parameters in Anemic Pulmonary Tuberculosis Patients (ATT without Ginger Supplementation)

Hb (g/dL)	11.14 ± 1.06	11.61 ± 1.18	9.13	< 0.001
CRP (µg/mL)	37.36 ± 5.73	26.87 ± 4.73	17.37	< 0.001
Ferritin (ng/mL)	378.12 ± 73.34	315 ± 60.49	8.94	< 0.001
Serum Iron (µmol/L)	5.00 ± 2.54	6.34 ± 2.48	13.93	< 0.001
TIBC (µg/dL)	198.56 ± 46.97	284.46 ± 46.08	11.83	< 0.001

Post treatment (30th days) value of parameters in study groups (GR- A & GR- B)

Both ginger supplemented (GR- A) as well as non-supplemented group (GR-B) causes significant decrease ($p < 0.001$) in the mean level of C-reactive protein and ferritin and increase in the level of hemoglobin (Hb) on 30th day **(Table-2 and 3)**. But the improvement was more marked in ginger supplemented group (GR- A).

Table 4: reveals that ginger supplemented group (GR- A) causes more percentage decrease in the level of C-reactive protein, ferritin and rise in the level of hemoglobin in comparison to ginger non supplemented group (GR-B). This indicates that ginger was effective as a supplement with anti-tubercular treatment.

Percentage change in level of parameters in different groups			
Parameter	ATT With ginger (GR- A)	ATT without ginger (GR-B)	Percentage difference
CRP **(µg/mL)**	45.59% ↓	28.07% ↓	17.52%
Ferritin **(ng/mL)**	21.77% ↓	16.69% ↓	5.08%
Hb**(g/dL)**	5.6 % ↑	4.21% ↑	1.39%

4. Discussion

4.1 Before treatment (zero days) values of different parameters

A highly significant decrease in hemoglobin level was observed in TB with anemia as compared to control subjects **(Table 1).** The patients having increased CRP level were less hemoglobin, this indicates that severity of anemia is associated with rise in CRP level.

The previous reports also showed the fall in hemoglobin level in anemic pulmonary TB patients [16, 17, 18]. In the present study majority of anemic TB patients had normocytic- normochromic anemia and few cases were of normocytic & hypo chromic anemia. The subnormal value of hemoglobin level was found in TB with anemia patients, which might be associated with the underlying chronic disease condition which slowly progress in the TB patients due to poor nutrition, anorexia, increased acute phase response and severity of the disease that causes blunted erythropoietin response which in turn causes iron deregulation and anemia. A highly significant decrease in Serum iron (SI) and TIBC was observed in TB with anemia as compared to control subjects **(Table 1).**

Earlier it was observed by different workers a low iron level in pulmonary tuberculosispatients [19]. The TIBC acted as negative acute phase reactants so the level of TIBC was found to be decreased from the level of control group [20]. The decreased level of TIBC might have been due to acute phase response [21].The reason for low iron & low TIBC in pulmonary tuberculosis was due to the disturbances in iron homeostasis.

In pulmonary tuberculosis patients a highly significant rise was noted in serum levels of C-reactive proteins (CRP) and Ferritin (FRT) as compared to control group **(Table 1). Similar finding were made by other workers** [22], [23].

The previous report also showed that in pulmonary tuberculosis ferritin synthesis is stimulated by the inflammatory process [24], [25], [26].

The present study reveals that inflammation and acute phase response interact with iron metabolism. Since anemia of pulmonary tuberculosis is multifactorial in origin as like anemia of chronic disease which affect iron metabolism directly and indirectly depending upon the severity of disease condition. In case of anemic tuberculosis patients, more rise in CRP leads to blunted erythropoietin resistance which is responsible for anemic condition. Since Ferritin synthesis is stimulated by inflammatory process regardless of iron status, serum ferritin, a noninvasive indicator of iron store is an acute phase response. In fact this acute phase response is thought to be beneficial to the organism by preventing microbial growth and helping to restore homeostasis.

4.2 Post Treatment (30th days) Value of Different Parameter with and without Ginger Supplementation

Synergistic effect of ATT with ginger for 30 days causes significant fall in C-reactive protein & ferritin level and rise in hemoglobin **(Table 2)**. ATT without ginger supplementation for 30 days also produced significant fall in C-reactive protein and ferritin and rise in hemoglobin (**Table 3)** but the value were less significant in comparison to ginger supplemented group.

The combined effect of ATT with ginger supplementation for 30 days in (GR-A) raised the hemoglobin level by 5.6 % and decreased the CRP, ferritin levels by 45.59% and 21.77% respectively while the ATT drug alone in (GR-B) increased the hemoglobin level by 4.21% and decreased C-reactive protein & ferritin levels by 28.07% & 16.69% respectively **(Table 4)**.

Use of powdered ginger for 3-month to 2.5-year period in Rheumatoid arthritis (RA) and Osteoarthritis (OA) patients, reduced pain and inflammation in 75% patients without any adverse effect and observed ginger is an anti-inflammatory agent [27].

Ginger extract-HAPC (100 microg/ml) significantly inhibited the activation of TNF-alpha and COX-2 expression in human synoviocytes with suppression of TNF-alpha and PGE-2 through NF-kB [28].

Phytomedicine have more beneficial effect than their synthetic counterparts through being safer, acceptable, affordable, culturally compatible and suitable for chronic disease treatments [29].

6- gingerol acts as an anti-inflammatory compound and used to treat inflammation without interfering with antigen presenting function of macrophages [30].

In anemic pulmonary tuberculosis patients anemia is associated with disturbance of iron metabolism due to alteration in acute phase proteins. For the correction of anemia iron supplementation is a usual practice but such supplementation has its own limitations. Overload of iron causes iron toxicity thus monitoring of serum iron become essential in such patients. Moreover iron generates free radicals which are harmful for the body.

The present study revealed that Synthetic and chemical drug can have greater and quicker effect and risks. Ginger being a rich

source of iron and by its anti-inflammatory and antimicrobial action it helps to reduce anti-inflammatory response and increase iron absorption from the gut .Ginger along with the ATT can help to reduce the load of drug in TB patients, moreover the consumption of ginger for a long period of time in such patients might be helpful to prevent relapse of the disease. Combination of 3 gm. ginger powder/day orally with ATT could be valuable to combat TB Patient with various complications rather than only ATT. Further trials in humans are required to determine the efficacy of ginger (one or more of its constituents), and to study what, if any, beneficial or adverse effects are observed if consume over a long period of time.

5. Conclusion

The result of previous and present study revealed that ginger reduces the level of Acute Phase Proteins mainly CRP by down regulating proinflammatory cytokine level, which in turn improved erythropoiesis in anemic pulmonary tuberculosis patients. Due to broad spectrum of biological function, ginger can safely be included in the standard anti-tubercular treatment in case of TB patients. Ginger synergistically cures the disease state.

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7. Reference:

1. WHO Tuberculosis Factsheet; March 2010
2. Jurado RI. Iron, infection, and anemia of inflammation. Clin Infect Dis 1997;25, 888–895.
3. Andrzez. Molecular Biology, Biochemistry & Clinical Application: CRC Press, 1993.
4. Goldenberg AS, Hematological abnormalities and mycobacterial infections. In Tuberculosis, 1996 pp. 645– 652.
5. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005; **352**: 1011-23.
6. Andrews NC, Disorders of iron metabolism. New Eng J Med. 1999**; 341**, 1986–1995.
7. Lyudmila G, Nikolaeva TV, Maystat VS, Pylypchuk YL, Volyanskii VM, F, Galyna A, Kutsyna. Cytokine profiles of HIV patients with pulmonary tuberculosis resulting from adjunct immunotherapy with herbal phytoconcentratesDzherelo and AneminCytokine. 2008; 44 (3), 392 -396.]
8. Hiserodt RD, Franzblau, SG, Rosen RT.. Isolation of 6-, 8-, 10-Gingerol from Ginger Rhizome by HPLC and Preliminary Evaluation of Inhibition of *Mycobacterium* avium and *Mycobacterium* tuberculosis, J. Agric Food Chem.1998; 46(7): 2504–8.
9. Kim JK, Kim Y Na, KM Surh, YJ, T.Y; 2007. [6]-Gingerol prevents UVB-induced ROS production and COX-2 expression in vitro and in vivo. Free Radic. Res. **41**, 603–614.
10. Grzanna R, LindmarkL,Frondoza CG. Ginger – an herbal medicinal product with broad anti-inflammatory action. J Med.Food2005; 8,125- 132.
11. Daves SJ Faujdar, P Kumar, P Gupta, R Das, GParasher, D. S. Chauhan, M. Natrajan, U.D Gupta and V.M. Katoch. Comprative growth pattern of multi drug resistance versus susceptible isolates of Mycobacterium tuberculosis in mice lungs. Indian.J.Med.Res2009; 130 (1) :58-62
12. Iron deficiency anemia. WHO Tech Rep Ser 1959; 182:4
13. Ronald H, Clin chem.1983; 2916 : 1109 – 1113
14. Siedel, J.Clin Chem. (1984); 30:975.
15. Tietz NW. Textbook of Clinical Chemistry, Philadelphia, PA: WB Saunders; 1701-1703; 1999.
16. Baynes RD, Flax H, Bothwell TH, Bezwoda WR, MacPhail AP, Atkinson P, Lewis D. Haematological and iron-related measurementsin active pulmonary tuberculosis. Scand J Haematol 1986; **36** (3): 280-7.
17. Singh KJ, G Ahuwalia SK, R Saxena, V.P.Chaudhary and T. Anant. Significances of hematological manifestation in patients with tuberculosis. J.Assoc. Physicians India. 2001; 49: 790-794.
18. Al Omar IA, Al Ashban RM and Shah AH. Hematological abnormalities in Saudis suffering from pulmonary tuberculosis and their response to the treatment. Research Journal of pharmacology. 2009; 3 (4):78 – 85.
19. Karyadi KE, Schultink JW, Nelwan RHH, Gross R, Amin Z, Dolmans WMN et al. Poor micronutrients status of active pulmonary tuberculosis patients and matched controls in Indonesia. J. Nutr. 2000; 130: 2953 – 8.
20. Frank H. Wians, Jill E. Urban, Joshef H. Keffer and Steven H. Kroft. Discriminating between Iron Deficiency Anemia and Anemia of Chronic Disease using Traditional Indices of Iron Status VS Transferrin Receptor Concentration. Am. J ClinPathol 2001; 115: 112 – 118
21. Fleck A,Myers MA. Diagnostic and prognostic significance of acute phase proteins. In the Acute Phase Response to Injury and Infection. 1985: 249-271 (AH Gordon and A Koj,editors). Amsterdam: Elsevier science publishers.
22. De Beer FC, Nel AE, Gie RP, Donald PR, Strachan AF.Serum amyloid A protein and C-reactive protein levels in pulmonary tuberculosis: relationship to amyloidosis.Thorax. 1984; 39(3):196-200.
23. Rao Sukhesh**,** BernhardtVidya. Serum C - reactive protein in Pulmonary Tuberculosis: Correlation with Bacteriological Load and Extent of Disease. Infectious Diseases in Clinical Practice: 2009; 17 (5):314-316.
24. Henderson A. Ferritin levels in patients with microcytic anaemia complicating pulmonary tuberculosis.Tubercle. 1984; 65 (3):185-9.
25. Morris CD, Bird AR, Nell H. The haematological and biochemical changes in severe pulmonary tuberculosis. Q J Med 1989;73: 1151-9.
26. HenrikFriss, Nyagosya Range, Camilla BraendgaardKristensen, Pernillekaestel.Acute phase response and iron status marker study in Mwanza, Tanzania. British journal of Nutrition 2009; 102: 310- 317.
27. Srivastava KC, Mustafa T. Ginger (Zingiberofficinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1992; 39: 342- 8.
28. Frondoza CG, Sohrabi A et al. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cell DevBiol Anim.2004;40(3-4):95-101.
29. R. N. Okigbo and E.C. Mmeka. An appraisal of Phytomedicine in Africa. KMITL Sci. Tech J. 2006; 6 (2): 83 – 94.
30. Tripathi S, Maier KG, Bruch D, Kittur DS. Effect of 6-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. J. Surg. Res.2007; 138 (2), 209- 213.