A Pilot Trial of Jawarish Amla as Adjuvant to Anti-Tubercular Treatment Drugs for Control of Adverse Reactions in DOTS Regime in Pulmonary TB

Arish Mohammad Khan Sherwani, MD[1]

Mohammad Zulkifle, MD[2]

Rehmatulla, MD[3]

[1]*Department of Preventative and Social Medicine, National Institute of Unani Medicine, Bangalore, India*

[2]*Department of Fundamentals of Unani Medicine, National Institute of Unani Medicine, Bangalore, India*

[3]*Ministry of Health and Family Welfare, Karnataka State Government, Bangalore, India*

Abstract

Background and objectives: One of the greatest challenges of health care systems at the dawn of the 21st century is tuberculosis (TB). Drug resistant strains of TB are becoming a global public health risk. These strains commonly appear due to faulty therapies. Patients frequently stop treatment due to the toxicity of anti-tubercular treatment (ATT) drugs. *Amla* (*Emblica officinalis*) is a well-known Unani single drug. *Jawarish amla* is a Unani compound formulation which is commonly used to administer *amla*. This study tested the efficacy of *Jawarish amla* as an adjuvant to ATT drugs in reducing their side effects.

Methodology: Half of forty eligible pulmonary tuberculosis patients were randomly assigned to Test (Group B) and the other half to Control (Group A). Six grams of *Jawarish amla* twice daily was administered to the test group, and the same dosage of placebo was administered to control group along with directly observed treatment, short course chemotherapy (DOTS) for 60 days. Fisher exact test and paired t-test were applied for efficacy evaluation. Grading of symptoms was done to assess the toxicity of ATT and outcome of the adjuvant.

Results and discussion: Significant improvements were observed in almost all subjective and objective parameters. The exceptions were serum creatine and serum uric acid, which showed non-significant slight elevations within normal limits.

Conclusion: *Jawarish amla* was ascertained to be safe and effective adjuvant of DOTS in combating the adverse effects of ATT drugs.

Key words: Pulmonary Tuberculosis; Side Effects; Drug Resistance; Herbal Medicine; Adverse Reaction; *Jawarish Amla*

Correspondence should be directed to

Arish Mohammad Khan Sherwani, MD

arish_sherwani@yahoo.co.in

Introduction

About one third of the world population, about two billion people, is infected with tubercle bacilli. It is estimated that about nine million people develop tuberculosis every year. By 2020, another 200 million people are expected to become sick, and about 70 million will die from tuberculosis (TB). TB has been a major communicable tragedy for centuries and is the prime cause of morbidity and mortality in patients with human immunodeficiency virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS).[1,2,3] It is estimated that 2.5 million people are infected with HIV in India. Considering 40% of the total population of India is infected with *Mycobacterium tuberculosis*, an estimated 1 million persons are co-infected with TB and HIV. HIV is the most powerful risk factor for the progression of TB infection to TB disease. It is also the leading cause of death in People Living with HIV/AIDS (PLHA).

Under directly observed treatment, short course chemotherapy (DOTS), the patient is observed while taking medication. This observation helps ensure that the correct dosage of the drug is taken at the right time. It also ascertains that the patient does not stop the treatment midway. When used properly, a course of DOTS cures over 80% of patients, striking a significant blow against TB worldwide.

A number of dropouts are recorded, mainly because of the side effects of the anti tubercular treatment (ATT) drugs used in DOTS. Isoniazid causes peripheral neuropathy and hepatitis. Rifampicin causes loss of appetite, nausea and hepatitis. Ethambutol causes visual disturbances (poor vision and color perception). Pyrazinamide causes hepatitis and arthritis. The toxicity of drugs is the major reason for defaulting from treatment, which the Revised National Tuberculosis Control Programme defines as not taking anti-TB drugs for 2 months or more consecutively.[4,5] "Effective use of first line drugs in every category I and category II patients [sic] as suggested by DOTS strategy and ensuring adherence to a full course of treatment is [sic] the key to curing TB patients and preventing the emergence of drug resistance."[6]

A pharmacologically multi-potent herbal adjuvant drug which can also combat the adverse effects of DOTS chemotherapy and improve the patient's compliance with DOTS would be of vital importance. *Jawarish amla* as an adjuvant therapy may increase the efficiency of DOTS therapy, reduce the number of drug resistance cases and side effects as well as reverse the consequences and rejuvenate body power. A recent study of *Jawarish amla* "showed potential to provide protection against toxic effects of cyclophosphamide in tumour bearing mice."[7] Thus a study using *Jawarish amla,* an Unani adjuvant compound formulation, has been undertaken to evaluate its efficacy in combating the side effects of ATT drugs, reversing the adverse consequences of DOTS therapy, boosting general immunity and facilitating a complete recovery from TB.

Table 1 includes a list of all Unani medical terms used in this paper.

Materials and Methods

The present study was designed as a single-blinded randomized controlled, concurrent parallel, comparative, adjuvant clinical trial, conducted at the National Institute of Unani Medicine (NIUM) Hospital, Bangalore, to evaluate the efficacy of *Jawarish amla as* an adjuvant in combating the side effects of ATT among patients of pulmonary TB on DOTS regime. The study duration was from March 2010 to March 2011.

All pulmonary tuberculosis patients on DOTS, age between 15-60 years and patients of either sex were eligible for inclusion in the study. Patients diagnosed with diabetes mellitus, HIV/AIDS or hormonal disorders, patients on corticosteroid therapy, extra pulmonary tuberculosis patients, patients with severe disability and patients not

willing to give consent were excluded from the study.

Ethical clearance was obtained from the institutional ethical committee for biomedical sciences at the National Institute of Unani Medicine (NIUM), Bangalore. There were 54 enrolled patients. Of the fourteen cases who could not complete the study, one patient of the placebo group died without any known immediate cause. Ten others dropped out from the study within one month of the trial. Three patients of the test group who came from other places returned to their homes for completion of DOTS therapy as they were unable to in Bangalore until the completion of the DOTS regime. Fourteen cases did not complete the study. The remaining 40 patients were equally randomized and matched into Test Group B, DOTS plus adjuvant drug, and Control Group A, DOTS plus adjuvant placebo, by table of random numbers calculated by Stat Trek's Random Number Generator.

Selection Criteria for Adjuvant Drug

The fruit *amla* is used for many ailments, particularly in South India. It is easily available and cheap. Retrolective survey of ancient literature and scientific studies revealed that *amla* (*Emblica officinalis*) is an antipyretic, hepato-protective, appetizer, anti-tussive, nervine tonic, antihemorrhagic, anti-inflammatory drug[7] which strengthens the vital organs and stomach and enhances vision. It is also a good blood purifier which inhibits production of morbid *balgham* and *sauda*. *Amla* is a well known Unani single drug. *Amla* is the richest source of natural heat stable vitamin C. It is a powerful antioxidant and boosts immunity. It restores vitality and rejuvenates all of the vital organs.[9]

Jawarish amla is a sweet, semi-solid and granular unani compound formulation. Its chief ingredient is *amla* (*Emblica officinalis*), which is processed in cow milk and sugar. The term *Jawarish* is derived from the Persian word *gowarish*, which means the granular semisolid that tends to stay longer in the gastrointestinal tract to enhance its digestive power and to potentiate liver.

Administration of Conventional DOTS and Adjuvant Regime

Patient-friendly boxes were prepared. They consisted of two kinds of pouches for intensive or initial phase (12 blisters) and continuous phase (48 blisters) of treatment. The pouches were administered for six or eight months at the patients' primary health centers (PHCs), which are the community health centers or nearby hospitals to which patients would come three times per week during the initial phase and once weekly during the continuous phase. PHCs are generally one to two kilometers from the patients' homes.

During the initial two month intensive phase, patients swallowed the drugs under the supervision of the doctors and drug providers at the time of their thrice weekly visits. In the subsequent continuous phase of TB treatment, patients received seven-day blister packs at their PHCs, and, after taking the initial day's dose at the PHC, take the remaining six days of medicine on their own.

All study participants from the various PHCs came to NIUM to receive the supply of adjuvant drug of either *Jawarish amla* or placebo, given in fifteen-day dose packs. Placebo of adjuvant drug was a sweet and morphologically similar, semisolid paste of similar color made by starch and sugar, given with the same dose of 6 grams, twice daily for two months. The adjuvant drug was taken 6 grams twice daily for two months after meal at their home. The *Jawarish amla* was prepared fresh and distributed at NIUM every two weeks to the patients during the two-month study period.

All clinically suspected outpatients and inpatients of NIUM with history of cough for more

Table 1. Unani Medical Terms

English and/or Latin	Transliteration	أردو
Indian Gooseberry (*Phyllanthus emblica*, syn. *Emblica officinalis*)	Amla	آملہ
Sweet, semi-solid and granular preparation of Unani compound formulation	Jawarish	جوارش
Gastric ulcer	quruhul meda	قروح المعدۃ
Hyperacidity	ḥumuzatul meda	حموضۃالمعدۃ
Headache	ṣuda	صداع
Biliary Diarrhea	ishāl-e ṣafravī	اسہال صفروی
Pulmonary tuberculosis	Diqq-e revi	دق ریوی
Phlegm (humor)	Balgham	بلغم
Black bile or melancholy (humor)	Sauda	سودا

than two weeks were investigated for pulmonary Koch's. Eligible patients were enrolled into the study with their written consent. All clinically suspect patients had chest x-rays (PA views) at NIUM. Two sputum samples (early morning and spot) were collected and sent to the designated microscopic centre, Leggere PHC, for acid-fast bacilli (AFB) examination as a routine diagnostic procedure. All diagnosed cases of pulmonary tuberculosis were advised to come for two week followup and adjuvant, *Jawarish Amla* or placebo, was prescribed, 6 grams twice daily for two months.

In India, patients diagnosed with TB and prescribed DOTS are provided with DOTS treatment cards. Each card contains a unique TB number and enables tracking of associated lab results and other case-related information. All patients' DOTS treatment cards were verified before enrolling in the study. The cards were photocopied and retained for authenticity.

Investigations were carried out for diagnosis, exclusion and assessment of the objective parameters in various treatment groups. Investigations done in every case included complete hemogram, erythrocyte sedimentation rate, fasting blood glucose, serum creatinine, serum uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), serum total bilirubin, HIV I & II, chest x-ray PA view and sputum smear test for AFB.

Investigations for objective evaluation were assessed at zero days (before starting) and on

60thday (after completion) of the treatment at NIUM. Investigations for exclusion and diagnostic criteria were taken at pre-treatment assessment. Sputum for AFB was examined before treatment and after completion of initial phase and continuous phase in the patients' respective health centers at regular standard intervals as a protocol of DOTS.

The study's parameters were subjective and objective. The subjective parameters were the adverse reactions the patients reported. Adverse reactions' severity was classified as minor, major and other. The minor reactions were nausea, vomiting, anorexia, abdominal pain, itching, rash, joint pain, and burning sensation in feet. The major reactions were jaundice, constipation, skin rash and flu syndrome. Other side effects were bitter taste, angina, diarrhea, sweating, insomnia and body pain.[10,11] Before starting treatment, each sign and symptom was recorded in the case report form for their grades at the initial visit. Any worsening or improvement in parameters was noted down at every follow-up visit until the end of the treatment.

The liver function tests alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin and the renal function tests serum creatinine and serum uric acid are objective parameters of DOTS toxicity.[4,12,13,14] These tests were administered for efficacy evaluation of adjuvant drug.

After 60 days of the treatment, the pre- and post- treatment values of different parameters (subjective and objective) were analyzed and subjected to comparisons and statistical analysis to evaluate the efficacy of the treatment. Patient's compliance to treatment and improvements in adverse reactions to the ATT treatment and in signs and symptoms of tuberculosis were closely watched throughout the study.

Paired t-test was applied to analyze the intra group comparison of pre- and post-treatment variables, and unpaired t-test and Fisher exact test was applied to compare inter groups after treatment variables. SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data. Results on continuous measurements are presented on mean ± SD (range) and results on categorical measurements were presented in Number (%). Significant figures were stated as p≤ 0.05.

The safety of the treatment was assessed clinically at every visit of follow up and discontinuation of study medication was the prime tool of safety measure. However, there was no such consequence observed which had negative impact on our study.

Results

Efficacy evaluation of Jawarish Amla on Subjective Parameters

The minor side effects of the incidence of nausea (p<0.001), vomiting (p<0.001), abdominal pain (p<0.001), itching (p<0.001) and burning sensation in feet (p<0.001) were significantly less in Group B than in Group A. The major side effects of the incidence of jaundice (p<0.001) and skin rashes (p=0.003) were significantly less in Group B than in Group B. No patient in Group B developed flu during the trial. All patients in Group B who began the trial with flu were relieved of its symptoms during the trial. In Group A, 6 patients developed the symptoms of flu, and they persisted throughout the therapy.

Other evaluated side effects included bitter taste, diarrhea, insomnia and body ache. Bitter taste was a very common problem among the studied patients and a common reason for them to abandon the DOTS regime. A significant (p<0.001) reduction in bitter taste occurred in Group B. All patients in Group A developed diarrhea during the course of DOTS regime. All patients of Group B

Table 2: Efficacy evaluation of *Jawarish Amla* on serum creatinine (mg/dl) (n=40)

Group	BT	AT	P value
Group A	0.87±0.1	0.94±0.12	0.067
Group B	0.87±0.2	0.88±0.12	1.000
P value	0.943	0.166	-

Table 3. Efficacy evaluation of *Jawarish Amla* on serum uric acid (mg/dl) (n=40)

Group	BT	AT	P value
Group A	5.35±1.4	5.89±1. 5	0.068
Group B	5.48±1.5	5.75±1.6	0.437
P value	0.770	0.772	-

Table 4: Efficacy evaluation of *Jawarish Amla* on liver function tests (n=40)

Liver Function Test	Group	BT	AT	P value
ALT IU/L	Group A	23.6±9	33.2±12.6	0.005
	Group B	44.6±63.40	23.8±8.2	0.140
	P value	0.152	0.008	
AST IU/L	Group A	22.30±11.20	39.00±22.95	0.001
	Group B	46.55±72.67	23.10±12.20	0.162
	P value	0.148	0.009	-
Alkaline Phosphatase IU/L	Group A	125.40±33.33	141.20±33.31	0.069
	Group B	158.95±73.16	118.60±29.68	0.036*
	P value	0.070+	0.029*	-
Total Bilirubin mg/dl	Group A	0.59±0.22	0.84±0.25	0.002**
	Group B	0.68±0.32	0.67±0.45	0.932
	P value	0.295	0.150	-

who had diarrhea got significant ($p<0.001$) relief. The incidence of insomnia ($p<0.001$) and body ache ($p<0.04$) was significantly less in Group B than in Group A.

Effect on sweating and joint pain was not statistically significant in test group, although it was clinically effective. This may be because of the small sample size.

In this study, the hepato-protective, gastrointestinal, skin and anti-inflammatory effects of the test drug are demonstrated. No clinically significant side effects were observed in test group, and overall compliance to the treatment was found excellent.

Efficacy evaluation of Jawarish Amla on Objective Parameters

Serum creatinine and serum uric acid levels after treatment were lower in Group B than in Group A, but the differences were not statistically

significant. Pre- and post-treatment values were within normal ranges. (Tables 2 and 3)

Over the course of treatment, average ALT decreased in Group B, but the decrease was not statistically significant. ALT in Group A showed a significant increase (p=0.005) pre- and post-treatment. Group B's ALT values were significantly lower after treatment than those of Group A (p=0.008) (Table 4).

Group A's AST values increased significantly pre- and post-treatment (p=0.001). The decrease in Group B's AST values was not statistically significant. Group B's AST values were significantly lower after treatment than those of Group A (p=0.009) (Table 4).

Group A's alkaline phosphatase values did not increase significantly pre- and post-treatment. The decrease in Group B's alkaline phosphatase values was statistically significant (p=0.036). Group B's alkaline phosphatase values were significantly lower after treatment than those of Group A (p=0.029) (Table 4).

Group A's total bilirubin values increased significantly pre- and post-treatment (p=0.002). The change in Group B's total bilirubin values was not statistically significant. Group B's total bilirubin values were not significantly lower after treatment than those of Group A (Table 4).

Discussion

The significantly lower incidence of nausea (p<0.001), abdominal pain (p<0.001) and bitter taste (p<0.001) may be due to the fact that *Jawarish amla* heals *quruh-e meda* (anti-peptic ulcer) and reduces *humuzat-e meda* (acidity).[8,15] *Amla* also has antispasmodic activity.[16] This may have contributed to the reduced abdominal pain. Likewise, *Jawarish amla* is anti-emetic,[17] and this may be the cause of the lower (p<0.001) incidence of vomiting. The lower incidence of itching (p<0.001*) and skin rashes (p=0.003) in Group B may be attributed to the blood purifying,[8] anti-

histaminic[16] and cooling and soothing[9] properties of *Jawarish amla.* These same cooling and soothing effects may have relived the symptom of burning sensation in feet (p<0.001).

Amla is a hepato-protective drug.[8,9] This may explain the reduced incidence of jaundice (p<0.001) as a major adverse reaction in Group B. Likewise, the ALT (p=0.008), AST (p=0.009) and alkaline phosphatase (p=0.029) values in Group B after treatment were significantly lower than those of Group A. Even though the difference in total bilirubin values after treatment between the groups was not significant, Group A's values increased during the ATT (p=0.002) while Group B's did not.

The reduction in flu-like syndrome in Group A may be attributed to the immunomodulatory, antioxidant, anti-inflammatory and antiviral properties of *amla*.[6,16] The reduced incidence of diarrhea may be attributed to the fact that *amla* stops biliary diarrhea (*ishāl-e ṣafravī*),[3] one of the types of *ishāl* (diarrhea).[15]

Insomnia was increased in Group A and decreased in Group B with p<0.001. This may be attributed to the strengthening effect on brain,[15] cooling and soothing[9] effects, reduction of *suda* and *humuzat-e meda*[14] and digestive properties[8] of *amla* and/or *Jawarish amla.* Body ache increased in Group A and decreased in Group B with p<0.04*. This may be attributed to the strengthening effect of *amla* and/or *Jawarish amla* on vital organs[9] and its anti-inflammatory[16] and analgesic activity.[15]

Conclusion

The overall effect of the test drug *Jawarish amla* was found quite encouraging in pulmonary tuberculosis (*diqq-e revi*). Significant improvement was observed in nausea, vomiting, anorexia, abdominal pain, itching, burning sensation in feet, jaundice, skin rashes, flu like syndrome, bitter taste, diarrhea, constipation, insomnia, body ache, ALT, AST, alkaline phosphatase and total bilirubin

in test group in comparison to control group.

The test drug in this study was safe and effective in checking the adverse effects of ATT drugs used in DOTS therapy. It may thus be an excellent adjuvant to DOTS in the community management of pulmonary tuberculosis (*diqq-e revi*). This adjuvant therapy should be selected for study involving a large sample size. If the results of this study are confirmed, it should then be implemented in India's Revised National Tuberculosis Control Programme (RNTCP) for checking the adverse reaction of DOTS and efficacy improvement.

Acknowledgement

References

1. Herzog H. History of tuberculosis. Respiration. 1998;65:5-15.

2. Abū-Marwān ibn Zuhr. Kitabut Taisir. New Delhi: CCRUM; 1986.

3. Kabeeruddin M. Hummiyat-e Qanoon. New Delhi: Aijaz Publishing House; 2007.

4. Awofeso N. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. Bull World Health Organ. 2008;86:B-D. http://dx.doi.org/10.2471/BLT.07.043802

5. Pandit N, Choudhary SK. A study of treatment compliance in directly observed therapy for tuberculosis. Indian J Community Med. 2006;31:241-3.

6. Thakur H. Drug resistance in tuberculosis control: a global and Indian situation. Journal of Preventative Medicine (Romania). 2008;16(3-4):3-9. http://bit.ly/WzF5Pw

7. Ahmad F, Rashid H, Bhatia K, et al. Modulatory effect of a Unani formulation (*Jawarish amla sada*) on cyclophosphamide-induced toxicity in tumour bearing mice. Br J Med Med Res. 2012;2:454-68.

8. Nantant mahattanapokai. Preparation and evaluation of emblica officinalis extract cream, A thesis submitted in partial fulfillment, for the degree of master of science in pharmacy (pharmaceutics) faculty of graduate studies, mahidol university 2003.

9. Ghani N. Khazayanul Advia. Vol I-IV. New Delhi: Idara Kitabush Shifa; YNM: 33-34, 187-189.

10. Koju D, Rao SB, Shrestha B, et al. Occurrence of side effects from anti-tuberculosis drugs in urban Nepalese population under DOTS treatment. Kathmandu University Journal of Science, Engineering And Technology. 2005;1. http://www.ku.edu.np/kuset/aej/dinesh.pdf

11. Zierski M, Bek E. Side-effects of drug regimens used in short-course regimens used in short-course chemotherapy for pulmonary tuberculosis: a controlled clinical study. Tubercle. 1980; 61:41-9. http://dx.doi.org/10.1016/0041-3879(80)90060-4

12. Durand F, Jebrak G, Pessayre D, et al. Hepatotoxcity of antitubercular treatments: Rationale for monitoring liver status. Drug Saf. 1996;15:394-405.

13. Sharma S K, Balamurugan A, Saha PK, et al. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med. 2002;166:916-9. http://dx.doi.org/10.1164/rccm.2108091

14. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and

pyrazimamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996; 9:2026-30.

15. Anonymous. The Unani Pharmacopeia. Part I. Vol 4; Ministry of Health and Family Welfare; Government of India, Dept of Ayush, 2007:5,6

16. Alternative-health.com [website on Internet]. Amla (*Emblica officinalis*): benefits and uses. [Accessed 2013-Jan-16] http://www.alternative-healthguide.com/ayurveda/amla_emblicaofficinalis.htm

17. Majoosi A. Kamilus Sana'ah (Urdu Translation by Kintoori GH). Vol.2 New Delhi: Idara Kitabus Shifa; 2010:155.