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Promising Herbals as Adjunctive to Standard Antituberculosis Therapy

Zulkifli Amin¹, Sari Purnama Hidayat¹
¹Division of Respiratory and Critical Illnes, Internal Medicine Departement, Faculty Medicine University of Indonesia, Jakarta, Indonesia

ABSTRACT

Background: Using ‘STOP TB’ strategy, World has succeed decreasing TB case and mortality rate. Nevertheless, both numbers remains high. By this study, we aimed to find any natural products could be used as adjunctive tuberculosis therapy in order to achieve better treatment result. Method: Review related articles found from Pubmed, Google Scholar, cochrane, and personal databases. Result: There was five natural products (Dzherelo, Curcumin, Cathecin, Jawarish amla, and Chinese herbal medicine) showed promising result when used as adjunctive to standard antituberculosis therapy. Dzherelo, curcumin, and CHM enhanced sputum conversion and improved lung lesions. Dzherelo and cathecin reduced free radicals agent. All herbals, except CHM is reported alleviating adverse antituberculosis drugs effects. Additionally, dzherelo also could modulated humoral and cellular immune system. Discussion: Inadequate drug regimens for treating TB cases, poor adherence due to long duration of therapy and adverse drug reaction, and uncompetent immune system can lead to treatment failed. Using herbal products as adjunctive tuberculosis therapy could improved tuberculosis treatment result. Conclusion: As adjuvant therapy, dzherelo and curcumin products are superior than others herbal products, but further investigation still needed.

Keywords: Natural products, Plants, Tuberculosis, Adjunctive therapy, Sputum conversion

INTRODUCTION

It has been more than two decades since the world started concerning about TB disease. TB mortality rate has decreased 47% and TB case rate has decreased 1.5-2%/year since 1990.¹² Nevertheless, both numbers remains very high.¹³ TB still ranks alongside HIV as a leading cause of death worldwide.¹

Since 2006, using DOTS strategy, newly diagnosed TB has achieved 86% of success treatment rate.¹³⁴ However, some regions still face difficulties to control tuberculosis. Their case rates were stagnant or decreased slower than expected.³ They reported high number of failed treated cases due to MDR TB and loss-to-follow up cases due to long duration treatment, drugs side effects, and other issues.¹⁵⁶ Those uncompleted treatment patients might became potential sources of new tuberculosis infections which increased the disease burden. Facing those problems, many studies aim to discover new regimens from natural products as an adjunctive to standard TB therapy which would more effective and safer than standard TB drugs alone.¹

Many natural products and their derivatives reported have antituberculosis activity, lower drugs adverse reaction, and modulate immune response.⁷ So by this paper, we would like to find any herbals that have been proved its efficacy on human trial as adjunctive tuberculosis therapy for newly diagnosed, as well as in previously treated or in MDR TB cases.

Current World’s Tuberculosis Burden

Based on 2015 Global Tuberculosis Report, estimated 13 millions TB cases around the world. With 9.6 millions incidence and 1.5 millions death every year. MDR-TB is predicted over 3.3% of new cases and 20% of previously treated cases.¹ During 2005-2010,
TB cases also increased alongside the number of HIV infected population. HIV related TB death accounted 33% among TB deaths and was the biggest portion among HIV deaths. Success tuberculosis treatment rate was also worse in HIV patients (73%) compared to non-HIV patients (88%). Those high prevalence and incidence of TB, emerging of MDR TB, and high HIV infections are major threats in controlling worldwide tuberculosis.

The succeed of controlling TB disease in last two decades proved that TB is a controlable disease. Most of TB disease (97% globally) are drug-susceptible. Based on cohort research (2013), treatment success rate reach out 86% among new and relaps cases. Meanwhile, MDR-TB is also reported by 153 countries with estimated around 480.000 cases. 9,7% among those are predicted have XDR-TB strains. Treatment success rate for MDR and XDR-TB patients remained consistently and miserably low, even with adequate resources for diagnose and therapy and high quality health care provider.

### Role of Herbal as Adjuctive Antituberculosis Therapy

Many herbals have been used by traditional health practitioner and herbalist for treating tuberculosis. However not many of them have been investigated for their efficacy, safety, and applicability in human. Investigating the last 10 years study, we found 5 natural products from 8 related articles have been proved its efficacy, safety, and applicability on clinical trials as adjuvant therapy to standard tuberculosis treatment. Those herbal products and plants extracts are presented in the table 1.

#### Table 1. Adjunctive Herbal on Standard Tuberculosis Therapy Significant Result

<table>
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<th>No</th>
<th>Plants/Products</th>
<th>Research</th>
<th>Result</th>
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<td>1</td>
<td>Dzherelo</td>
<td>Zaitzeva SI, et al (2009); open-label, newly diagnosed TB.</td>
<td>Sputum conversion*, Clinical features and respiratory function*; Better radiologically in 60 days†; Decrease bilirubin, AST, ALT*, Decrease urea level*, Oxidative stress marker*</td>
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<td>Nicolaeva LG, et al (2008); paired 60 pts TB/HIV cases: dzherelo, dzherelo-anemin, control</td>
<td>Adjuvant dzherelo: Increase IL2, suppress TNF-α.† Adjuvant dzherelo + anemin: Decrease IL-6, increase IFN-ϒ.†</td>
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<td>Arjanova, et al. (2009): open-label paired 40 TB/HIV pts w/o ARV</td>
<td>Culture conversion 3(16%) vs 12(67%); Healing pulmonary cavitation†; Increase body weight*</td>
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<td>4</td>
<td>Jawarish amla</td>
<td>Sherwani AMK, et al (2012) RCT, matched, blinded, TB cases</td>
<td>Lower Nausea*, Vomiting*, abdominal pain*, peripheral neuropathy*, jaundice*, skin rash†, bitter taste* Decrease AST†, ALT†, Alkaline Phophatase†</td>
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<td>5</td>
<td>Chinese herbal medicine</td>
<td>Shi GC, et al (2015) RCT, Newly diagnosed TB with DM</td>
<td>Sputum conversion†, Lung improvement†, Fasting plasma glucose*, 2-hours post-prandial plasma glucose†</td>
</tr>
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* = p<0.001, † = p<0.05
Dzherelo

Dzherelo is a concentrated aqueous alcohol extract from 27 species of medicinal plants. It has been approved by Ukrainian Ministry of Health in 1997, and placed as superior category of herbal supplement in 2006. Dzherelo has been sold in Ukraine and exported with price €10 or USD $11.3 for 30 ml.

Dzherelo eliminate *Mycobacterium tuberculosis*, proved by accelerating sputum conversion, improving chest image especially cavity closure, and also improving overall clinical features and respiratory function. Besides, it also reverse adverse antituberculosis drugs effect, such hepatotoxicity and renotoxicity. The efficacy is showed in both newly diagnosed TB and co-infection HIV-TB patients who commonly have worse result. This better result are related with better immune response as dzherelo could regulate both humoral and cellular immune response. Dzherelo roled in (1)higher IL-2 and IFN- which have role in accelerated mycobacterium elimination (2)supressed IL-6 which interrupt cellular immune response (3)lower TNF-α. The lower TNF-α usually related with worse result. However in Nikolaeva study, lower TNF-α precisely showed better clinical outcomes. This phenomenon is contradicted with old theory and still couldn’t be explained. Better cellular response was showed by significantly increased of CD3+, CD4, and CD3+HLA-DR+ (activated lymphocyte) in TB/HIV patients who even didn’t get any antiretroviral.

Anemin which is mentioned in Nikolaeva study is another phytoconcentrate used in Ukraine for anemia. All preparations of the products are also found in Dzherelo, except *Menyanthes trifoliate* which known as antiinflamatory herbs for chronic disease. Using this product additionally with dzherelo significantly increased IFN- and suppress IL-6 which did not significantly increased in only dzherello group.

*Curcuma Longa- Tinospora cordifolia*

Hepatotoxicity induced by antituberculosis drugs is reported in 11.5% in eastern region and 4.3% in western region. In high risk group, hepatotoxicity rate found 18.2%. *Curcuma longa* and *Tinospora cordifolia* firstly introduced as liverprotective herbs for improving liver function, protecting against toxic, and increasing protein synthesis. Curcumin reported safe for human consuming up to 12g/day orally.

Using single isolated plant extract shows lower efficacy than the combination. Adhvaryu study also using combination of *Curcuma longa* and *Tinospora cordifolia* for achieving better antituberculosis treatment result. The exact mechanism of this synergist is unknown. Suggesting multi-target action compounds on molecular level so that resorption rate and herbas pharmacokinetics are better. Adjusted with malnourished, low-weight population, Adhvaryu used 500 mg extract powder twice daily for each herbas which equivalent with six gram of crude herbas extracts. There haven’t any marketed herbal products contain the combination of 500 mg *Curcuma longa* and 500 mg *Tinospora cordifolia*. Products with almost similar ingredients is *Extrammune* from India, contains 250 mg *Curcuma Longa*, 250 mg *Tinospora cordifolia*, but with addition *Rubia cordifolia* and *Plumbago zeylanica*. It sold USD $6.95/30 tablets.

Cathecin

Cathecin is an active polyphenols derived from *Camellia sinensis* or popularly known as green tea. Cathecin has ability to scavenge active oxygen free radicals and protect cell damaged that induced by free radicals. It is a water soluable compound, metabolism by liver, and excrete in urine after 6-48 hours. No residual/metabolite accumulates in body.

Tuberculosis disease naturally augmented free radicals as macrophage eliminate mycobacterium by phagocytosis. Lipid peroxidase, nitrit oxide, sulfhidryl, and catalase are oxygen free radicals products which would damage tissues directly by chimical binding reaction. Cathecin as antioxidant works by reducing those products. It also increased SOD level, substance that roles in formation/building new tissues. It’s sold for USD $313-443 every 10 unit.

Jawarish Amla

Traditionally, amla is used as antipyretic, hepatoprotective, appetite, antitussive, nerve tonic, antihemorrhagic, and anti-inflammatory. To make jawarish amla, amla is processed with cow milk and sugar. Jawarish amla as adjuvant therapy could lower antituberculosis drugs adverse effects significantly by unexplained mechanism. It is believed have blood purifying, antihistamin, and cooling property which...
has role in reducing adverse antituberculosis drug symptoms.\textsuperscript{9} This products has market priced USD $1.5-2/100 gr.\textsuperscript{22-23}

**Traditional Chinese medicine**

Traditional chinese medicine has widely definition. In Shi GC study, traditional chinesse medicine was prepared in decoctition using Qi-boosting and Yin-nourishing concept and added to current antituberculosis therapy (3HRZE/6HER).\textsuperscript{24}

The decoction contained: Huangqi (Radix Astragali Mongolici) 30gr, Xuanshen (Radix Scrophulariae) 30gr, and Dihuang (Radix Rehmanniae) 30gr, Cangzhu (Rhizoma Atractylodis Lanceae) 10gr, Maidong (Radix Ophiopogonis Japonici) 10gr, Danggui (Radix Angelicae Sinensis) 10gr, Baishao (Radix Paeoniae Alba) 10gr, and Zhimu (Rhizoma Anemarrhenae) 6gr. Others herbals were also added according to patients symptoms.\textsuperscript{24}

Adjunctive TCM showed significant higher sputum conversion and lung improvement in TB comorbid DM patients. In the other side, fasting blood glucose and 2 hour post prandial blood glucose also better in treatment groups. Because it contained Huangqi (Radix Astragali Mongolici), Dihuang (Radix Rehmanniae), Xuanshen (Radix Scrophulariae), and Cangzhu (Rhizoma Atractylodis Lanceae) which usually prescribe for lowering blood and urine sugar in DM patients. Within the study, no serious adverse effect was observed.\textsuperscript{24}

**DISCUSSION**

Tuberculosis case and mortality rate have been decreased.\textsuperscript{1} Nevertheless, tuberculosis keep widely spread and infect global populations. Based on WHO report, tuberculosis is the most caused death of infectious disease either in HIV or non-HIV population.\textsuperscript{1,2} Taking standard antituberculosis treatment, patients are expected underwent sputum conversion so spreading potentiation may be lowered. However, not all treated patients may encounter sputum conversion. Besides, there are also some who do not complete the treatment. Adding adjuvant herbal products to standard antituberculosis therapy showed some benefits in tuberculosis management. There was five herbals that have gone through clinical trials which showed better tuberculosis treatment result (clinically and objectively) or lowered adverse tuberculosis drug reaction.

The better treatment result within newly diagnosed TB are shown in dzherelo, *Curcuma longa* with *Tinospora cordifolia*, and chinese herbal medicine groups. Adding those products may produce higher sputum conversion rate and radiologic and functional lung improvement. Curcuma was also effective for relaps and chronic tuberculosis, while dzherelo was also effective for HIV/TB population as shown in Nikolaeva and Arjanova study. Both products may improved overall functional status and reversed TB associated wasting syndrome by significantly increase body weight.

The others herbal, Catechin and Jawarish amla, only reported having antioxidant and reversed antituberculosis drugs adverse effects’ abilities. However, having those abilities, they may also have important roles. Oxygen free radical is related with severe lung damage, while severe adverse drugs effect made physician unable to prescribe adequate dosage of antituberculosis regimens which lead to treatment failed. Uncomfortable symptoms related to adverse effects such as nausea, abdominal pain, peripheral neuropathy, or even minor ones may brings inadherence to antituberculosis treatment. Therefore, even they don’t work directly against the disease, they are still advantageous as adjuvant therapy. Besides catechin and Jawarish amla, dzherelo also showed antioxidant activity. Both dzherelo and curcuma products also have protective ability (hepatoprotective and renoprotective) against antituberculosis drugs’ adverse effect.

HIV and DM are high risk comorbidities within TB disease. Inadequate immune response as in HIV patients could lead into treatment failure. TB with DM patients have morbidity 4.8 fold higher than in non-DM population. Both HIV and DM show higher rate of *Mycobacteria tuberculosis* discharges, delay sputum conversion, and drug resistant TB strains. Therefore, controlling DM and achieving better immune response are also important for succeeding tuberculosis therapy. Using dzherelo as adjuvant tuberculosis therapy in HIV patients resulted better both cellular and humoral immune response. While TCM used in Shi-GC study resulted better glycemic status index.

Using adjunctive herbal products to standard tuberculosis therapy may improve tuberculosis treatment result. However, other psycho-socio-economic problems also have potential roles in succeeding TB therapy. Using DOTs strategy is supposed to address...
inadherence patients problems. But in reality, not all regions could provide volunteers to observed patients’ therapy directly. Instead they use family members as volunteers which in our experience was as ineffective as using no volunteers. Modeled after USA, using CDC tuberculosis law may became a promising strategy. If patient refuses treatment, he/she may be ordered by a court to remain isolated until no longer considered a threat to public health.  

However implemented this strategy globally may need large efforts, especially in high burden countries.

**CONCLUSION**

Dzherelo and combination curcuma product is more superior than three others herbals. Using combinations two or more herbal extracts, like in dzherelo and curcuma, would result in better efficacy than single isolated plants. However, before implemented, further studies still required in various-bigger population and longer duration. Besides, others strategies should also be thought in order to deal with psycho-socio-economic problems.

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