

Systematic Review

CASTOR PLANT (*Ricinus communis* L.) LEAF EXTRACT AS POTENTIAL ANTIBACTERIAL AGAINST THE GROWTH OF *Mycobacterium tuberculosis*

Fikriaddin Syafiq Istaufa¹, Yoyok Subagio², Irma Suswati³, Isbandiyah⁴

¹Medical Program, Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, Indonesia

²Department of Neurosurgery, Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, Indonesia

³Department of Microbiology, Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, Indonesia

⁴Department of Internal Medicine, Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, Indonesia

Mycobacterium tuberculosis is the cause of pulmonary tuberculosis that can reduce human health. In the therapy of the disease, patients can develop resistance to tuberculosis drugs. Based on the 2015 health profiles of Indonesia, 15,380 people were suspected to have multidrug-resistant tuberculosis (MDR-TB), while 1,860 people were confirmed patients with MDR-TB. There is a need for innovation to develop the latest treatments using natural ingredients, one of which is castor plant (*Ricinus communis* L.) that contains antibacterial compounds against *Mycobacterium tuberculosis*. This study aimed to understand the antimicrobial potential of castor plant (*Ricinus communis* L.) leaf extract against the growth of *Mycobacterium tuberculosis*. This scientific paper was a quantitative systematic review study. Literature in the form of journal articles and books were obtained through search engines, i.e. ebook database, Google Scholar, Cochrane, Wiley, and PubMed. The results of the literature source search were 19 journal articles and 4 ebooks, as well as 4 journal articles that were in accordance with the title of this literature review and discussed the effects of castor plants on the growth of *Mycobacterium tuberculosis*. The results of the analysis showed that castor plant (*Ricinus communis* L.) leaf extract has the potential in the antibacterial activity against the growth of *Mycobacterium tuberculosis* because it contains phytochemicals in the form of flavonoids, saponins, alkaloids, tannins, and fatty acid amides derived from ricinoleic acid as the main constituent of castor plants (*Ricinus communis* L.). There is antimicrobial potential for castor plant (*Ricinus communis* L.) leaf extract against the growth of *Mycobacterium tuberculosis*.

Keywords: Castor plant leaf; minimal inhibitory levels; *Ricinus communis* L.; lung health, *Mycobacterium tuberculosis*; tuberculosis

Correspondence: Fikriaddin Syafiq Istaufa, Medical Program, Faculty of Medicine, Universitas Muhammadiyah Malang, Malang, Indonesia. Email: fikrifromeastjava@gmail.com; fikriaddin@webmail.umm.ac.id

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Hi j ni j tu

1. Patients experiencing failure of first-line drug and developing multidrug resistant tuberculosis (MDR-TB) has increased throughout 2011-2015.
2. Castor plant leaf extract (*Ricinus communis* L.) has an antibacterial potential against the growth of *Mycobacterium tuberculosis* bacteria.

INTRODUCTION

Mycobacterium tuberculosis is one of the most dangerous Gram-positive pathogens that cause tuberculosis (TB) (Aljanaby et al. 2022). It is one of the deadliest bacteria and the main causative agent of TB, one of the most dangerous infections that has killed thousands of people worldwide because the bacteria grow slowly and early diagnosis for prevention is difficult (Rabahi et al. 2017, Ekawati 2018, Gopaldaswamy et al. 2020). Statistics showed that one-third of the world population has underlying TB infection (Houben & Dodd 2016). Globally, more than

a million people die each year as a result of the active disease, making it the second leading cause of death worldwide after the human immunodeficiency virus (MacNeil et al. 2020). According to the 2015 report of the World Health Organization (2015), the estimation of new TB cases was a million per year (399 per 100,000 population), with 100,000 deaths per year (41 per 100,000 population). The estimated number of human immunodeficiency virus (HIV)-positive TB was 63,000 cases (25 per 100,000 population). The Case Notification Rate (CNR) of all reported cases was 129 per 100,000 inhabitants. The total number of cases was 324,539, of which 314,965 were new cases (Indonesian

Ministry of Health 2016). In 2017, the number of new TB cases in Indonesia was 420,994. Based on gender, the number of new TB cases in 2017 was 1.4 times greater in men than in women. A prevalence survey, with a ratio of men and women, revealed that men are three times more at risk of TB compared to women because they are more exposed to TB risk factors, such as smoking and non-compliance of medication. The survey found that 68.5% of the male participants smoked, while only 3.7% of the female participants smoked (Indonesian Ministry of Health 2018).

The main symptoms of TB patients are hunger, fever, weight loss, drenching night sweats, feeling very tired or lacking energy, cough, and weight loss. Routine laboratory tests are rarely helpful in diagnosing TB (Lyon & Rossman 2017, Usmani et al. 2018). The nature of the disease is progressive chronic and its treatment takes as long as six months, with drug administration in the initial two months using isoniazid, rifampicin, and pyrazinamide. In the next four months, the treatment continued with drug administration using isoniazid and rifampicin (Rabahi et al. 2017). In the recovery of patient after receiving therapy for six months, some experience therapeutic failure or TB drug resistance, including mono-resistance, polyresistance, multi-drug resistance (MDR), extensively drug resistance (XDR), and rifampicin resistance (Velayati & Farnia 2016, Manson et al. 2017, Esteban & García-Coca 2018). In multidrug-resistant tuberculosis (MDR-TB) cases recorded in 2015, there were 15,380 suspects and 1,860 confirmed patients (Indonesian Ministry of Health 2016).

Medicinal plants offer great hope of meeting the needs of treatment and have been used for centuries to treat a wide variety of ailments. Recently, several reports and reviews of medicinal plants and natural products with anti-mycobacterial activity have been published. Medicinal plants contain compounds that may act as natural antitubercular agents in tubercular activity, such as alkaloids, peptides, tannins, phenols, quinones, and triterpenoids (Copp 2003, Okunade et al. 2004, Arya 2011, Rashid et al. 2015). Sixty plant species were studied for TB treatment, and 90 for leprosy treatment. In the Ayurvedic system, they have potential against tuberculosis, leprosy, and related disorders (Collins & Franzblau 1997).

The treatment of TB disease using medicinal plants is required. There is a need for innovation to develop the latest treatments using castor plants (*Ricinus communis* L.). Research on the utilization of castor plants are still few and rarely done. The use of castor plant leaves offered a potential of antimicrobial (Suvarna et al. 2018, Ghramh et al. 2019). Phytochemical analysis on castor plant (*Ricinus communis* L.) leaves revealed compounds that include tannins, saponins, alkaloids, and flavonoids, which are the basic properties of medicinal plants and the primary ingredients for the production of new drugs (Kumar 2017, Suurbaar et al.

2017, Azmy 2020). In previous studies, *Ricinus communis* L. leaf extracts were dissolved in water and partitioned using n-hexane to produce soluble n-hexane, then tested on *Mycobacterium tuberculosis* H37Rv (sensitive to all first-line drugs) and obtained a minimum inhibitory level (MIL) of 10 mg/mL (Ullah et al. 2017).

MATERIALS AND METHODS

The data search used a database of ebooks, Google Scholar, Cochrane, Wiley, and PubMed with the keywords "*Ricinus communis* L. + anti microbe", "*Ricinus communis* L. + anti-bacterial", "*Ricinus communis* L. + *Mycobacterium tuberculosis*", "extract leaf *Ricinus communis* L. + *Mycobacterium tuberculosis*", "castor + *Mycobacterium tuberculosis*", "extract leaf castor + *Mycobacterium tuberculosis*", "*Mycobacterium tuberculosis*" to collect literature from 2000 to 2021 for systematic review. The criteria for journal articles collected were as follows: 1) full text journal articles, 2) research on castor (*Ricinus communis* L.) as an antimicrobial and anti-*Mycobacterium tuberculosis*, 3) contain information about castor plant (*Ricinus communis* L.), 4) contain information about *Mycobacterium tuberculosis*, 5) literature in the form of qualitative, quantitative, and mixed method studies, 6) articles from quartile 1-4 journals.

The literature search resulted in 19 journal articles and 4 ebooks. Among journal articles that were in accordance with the title of this literature review, 4 articles discussed the effects of castor plants on the growth of *Mycobacterium tuberculosis*, while 9 articles discussed taxonomy, phytochemical content, and morphology in castor (*Ricinus communis* L.). There were 5 journals and 4 ebooks that discussed taxonomy, morphology, culture methods, and identification methods of *Mycobacterium tuberculosis*. There was also an article that discussed the effect of castor (*Ricinus communis* L.) leaf extract on minimum inhibitory levels of *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *K. pneumoniae*.

RESULTS

Mycobacterium tuberculosis is a species of pathogenic bacteria in the Mycobacteriaceae family (Gupta et al. 2018). It is the causative agent of tuberculosis with a high mortality rate in Indonesia. Data recorded from 2011 to 2015 showed that there were increases of MDR-TB suspects from 1,255 in 2011 to 2,441 in 2012, 3,833 in 2013, 9,399 in 2014, and 15,380 in 2015. Whereas, confirmed patients with MDR-TB were 216 in 2011, 460 in 2012, 1094 in 2013, 1,752 in 2014, and 1,860 in 2015. It indicated that there was a high increase of MDR-TB cases from 2011 to 2015 in patients who failed first-line drug therapy and caused them to develop MDR-TB (Pfyffer 2015, Indonesian Ministry of Health 2016).

The growth of *Mycobacterium tuberculosis* in adults is a slowly progressive process characterized by chronic inflammation, caseation, and formation of cavities. The central nuclei can rupture into the bronchi, allowing large numbers of organisms to spread to other areas of the lungs and become aerosolized with coughing, thereby infecting others (Barbier & Wirth 2016). Mycobacteria are aerobic, although some species can grow under a reduced O₂ atmosphere. The high complex lipid content of the cell wall prevents access to common aniline dyes. Although not directly stained by the Gram method, mycobacteria are usually considered Gram-positive. When stained by special procedures (e.g. Ziehl-Neelsen stain), mycobacteria were not easily decolorized, even with acid-alcohol. Compared to other bacteria, the growth of most mycobacterial species was slow, up to 20 hours on commonly used media. A natural division existed between slow-growing and fast-growing mycobacterial species (Drapal & Fraser 2019). Slow-growing mycobacteria required more than seven days to colonize on solid media from aqueous inoculum under ideal culture conditions. Fast-growing mycobacteria took less than seven days when subcultured on Löwenstein-Jensen (LJ) medium, but took several weeks to emerge in primary culture from clinical specimens (Pfyffer 2015). The identification of *Mycobacterium tuberculosis* bacteria was conducted by taking pulmonary secretion specimens from the bronchial tree. This specimen was obtained from spontaneous sputum, induced sputum, gastric lavage (for children or seriously ill patients who did not produce sputum), bronchoalveolar lavage (BAL), and transtracheal aspiration (endotracheal tube) (Mertaniasih 2019). The identification of *Mycobacterium tuberculosis* bacteria was also performed through microscopic examination of acid resistant rods, which included the standard Ziehl-Neelsen staining of sputum smear on standard binocular microscopes and fluorescein staining of sputum smear using microscopic fluorescents or LEDs (e.g. acridine orange) (Mertaniasih 2019).

Active plant extracts were tested using broth microdilution technique. The Middlebrook (MB) 7H9 broth was prepared and sterilized according to the manufacturer's instructions. A fresh working extract solution was prepared by diluting the stock solution to a concentration ranging from 2.5 to 40 mg/mL and adding 5 L of mycobacterial sensitive strain, the inoculum H37Rv (104-105 CFU/mL). Experiments were carried out after incubation at 37°C for four weeks (Ullah et al. 2017). In a previous study, the leaf extract of *Ricinus communis* L. was dissolved in water and partitioned using n-hexane to produce soluble n-hexane and then tested on *Mycobacterium tuberculosis* H37RV (sensitive to all first-line drugs) (Ullah et al. 2017).

Table 1. Average number of colonies of *Mycobacterium tuberculosis* H37RV on *Ricinus communis* L. leaf extracts

	Method	Solvent	Concentrate	Colony Total Average
Ladda & Magdum (2012)	Dilution	Ethanol	100 µg/mL	20.33
			150 µg/mL	4.33
			200 µg/mL	0
		Acetone	100 µg/mL	17.33
			150 µg/mL	0
			200 µg/mL	0
Chloroform	100 µg/mL	55.66		
	150 µg/mL	36		
	200 µg/mL	18.33		

The fatty acid amides derived from ricinoleic acid were tested. Ricinoleic acid (C18:1, OH) or 12-hydroxy-9-cis-octadecenoic acid is a major constituent (80-90%) in the hydroxyl chain of castor (*Ricinus communis* L.) oil. The fatty acid amides derived from ricinoleic acid showed interesting results against tuberculosis strains. The compound ricinoleylpyrrolidilamide, (R, R)-12d, showed antitubercular activity, with a minimum inhibitory level of 12.5 g/mL for tension resistance (D'Oca et al. 2010). The results were expressed as the ratio of resistance compared to control cultures. Fourteen colonies of *Mycobacterium tuberculosis* H37RV were observed for the ethanolic extract of *Ricinus communis* L. at 100 g/mL, while ten colony counts were observed for the patient strain at 150 g/mL.

Methanol inhibited the growth of *Mycobacterium tuberculosis*, which interpreted as nitrate reductase assay (NRA), while acetone extract did not inhibit the growth of *Mycobacterium tuberculosis*. The methanol had antitubercular activity at 100 g/mL (Ladda et al. 2018). The MIC for the standard strain and patient strain was 100 g/mL and 150 g/mL respectively. The resistance ratio (RR) was found to be 1.5. Because the RR value was less than 2, it indicated that *Mycobacterium tuberculosis* was sensitive to ethanolic extracts. Thus, it was concluded that the ethanolic extract was sensitive to *Mycobacterium tuberculosis* through the resistance ratio method.

The solvent extract of castor (*Ricinus communis* L.) leaves indicated its effect in inhibiting *Mycobacterium tuberculosis* H37RV. *Mycobacterium tuberculosis* H37RV is a type of bacteria that infects human and causes tuberculosis. It is a type of bacteria that is sensitive to first-line drugs, which means that the bacteria can be treated with first-line tuberculosis drugs, such as rifamycin, isoniazid, pyrazinamide, streptomycin, and ethambutol. However, there was a rifampicin-resistant strain (TMC331) of *Mycobacterium tuberculosis* that was obtained from

multidrug-resistant patients (D'Oca et al. 2010, Ladda & Magdum 2012, Ullah et al. 2017, Ladda et al. 2018).

The phytochemical content of castor (*Ricinus communis* L.) leaf extract includes saponins, tannins, alkaloids, flavonoids, and ricinoleic acid (C18:1, OH) that could inhibit the growth of *Mycobacterium tuberculosis* (Kesumasari et al. 2018). Flavonoids were able to inhibit the synthesis of cellular nucleic acids by inhibiting the topoisomerase enzyme of *Mycobacterium tuberculosis*. Flavonoids were also able to inhibit the electron transport chain and ATP synthesis to disrupt the energy source for the cell's life, so that the cell died due to lack of energy (Górniak et al. 2019).

The minimum inhibitory levels of castor (*Ricinus communis* L.) leaf extract were assessed against *Mycobacterium tuberculosis* H37RV, as the bacteria sensitive to first-line drugs, using 200 µg/mL ethanol, 10,000 µg/mL n-hexane, 40,000 µg/mL ethyl acetate, 5,000 µg/mL chloroform, 150 µg/mL acetone, 100 µg/mL methanol, and fatty acid amides dissolved in 12.5 µg/mL dimethyl sulfoxide. Dimethyl sulfoxide extract showed that its MIC worked against *Mycobacterium tuberculosis* H37RV. Dimethyl sulfoxide is an organic solvent that can dissolve polar, non-polar, and semi-polar solvent compounds. Thus, the antitubercular activity only came from the phytochemical agents of castor (*Ricinus communis* L.) leaf extract. It showed that the solvent extract of castor plant (*Ricinus communis* L.) leaf extract had an effect in inhibiting *Mycobacterium tuberculosis* H37RV (D'Oca et al. 2010, Ladda & Magdum 2012, Ullah et al. 2017, Ladda et al. 2018).

Mycobacterium tuberculosis cell wall is composed of a layer of peptidoglycan, which is a complex polymer consisting of a series of N-acetylglucosamine acid and N-acetylmuramic acid arranged alternately. The structure of the cell wall was damaged by inhibiting its formation or by changing it after it was formed. Antimicrobial substances in the form of tannins at low concentrations inhibited the formation of glycoside bonds, so that the formation of cell walls was disrupted. Whereas, antimicrobial substances at high concentrations stopped the formation of cell walls (Maisetta et al. 2019). Alkaloids targeted the DNA topoisomerase I enzyme, inhibited the activity of *Mycobacterium tuberculosis* topoisomerase I (MtbTopoI) and protein synthesis, and single-stranded DNA division that caused cell damage and disrupted the cell's life process (García et al. 2018). The results showed that castor (*Ricinus communis* L.) leaf extract effectively inhibited the activity of *Mycobacterium tuberculosis*.

Research presented in this study only examined the minimum inhibitory levels of castor plant (*Ricinus communis* L.) extract against the growth of

Mycobacterium tuberculosis H37RV (sensitive to all first-line drugs). Therefore, there is a need for in vitro and in vivo experimental research on the potential of castor (*Ricinus communis* L.) leaf extract against the growth of *Mycobacterium tuberculosis* strains resistant to rifampicin (TMC331) and isoniazid (INH) using the disc diffusion method. The use of dimethyl sulfoxide as solvent is also recommended because it produced a more effective yield of castor plant (*Ricinus communis* L.) leaf extract to inhibit the growth of *Mycobacterium tuberculosis* H37RV (sensitive to all first-line drugs).

Strength and limitation

The castor leaf extract is one of the innovations in developing new medicines. Exploration of the antimicrobial potential of castor leaf extract (*Ricinus communis* L.) needs to be carried out further because castor leaf extract has the potential to inhibit the growth of *Mycobacterium tuberculosis*, the bacteria that cause TB disease in the future.

CONCLUSION

The analysis of the journal articles using a quantitative systematic review method showed that castor plant (*Ricinus communis* L.) has the potential to inhibit the growth activity of *Mycobacterium tuberculosis*. The extract contains flavonoids, saponins, tannins, alkaloids, and ricinoleic acid compounds that can damage the bonds in bacterial wall, disrupt the formation of energy in the form of ATP, inhibit the topoisomerase I enzyme and protein synthesis, and disrupt the DNA formation. The analysis of the in vitro experiment showed that the use of dimethyl sulfoxide as a solvent of castor plant (*Ricinus communis* L.) leaf extract had minimal inhibitory levels that were effective in inhibiting the activity of *Mycobacterium tuberculosis*.

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Conflict of interest

There were no conflict of interests.

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Author contribution

Fikriaddin Syafiq Istaufa collected the data and wrote this research manuscript. Yoyok Subagio collected the data. Irma Suswati and Isbandiyah checked the result article.

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