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Short Communication

Glucomannan is a promising isoniazid's enhancer that inducing macrophage phagocytosis

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Abstract

Isoniazid (INH) is a frontline antituberculosis agent effective against *Mycobacterium tuberculosis* (Mtb), but the increasing challenge of avoiding multidrug-resistant tuberculosis, including INH resistance, necessitates innovative approaches. This study focused on enhancing macrophage phagocytosis to overcome INH resistance. Glucomannan, an immunomodulatory polysaccharide, emerged as a potential macrophage activator. Our objective was to characterize the glucomannan-INH mixture and assess its impact on INH efficacy and macrophage activity. Detailed examination of the glucomannan from *Amorphophallus muelleri* (0.05%–0.2%) was performed in several methods. INH sensitivity tests were carried out with the Mtb strain H37RV on Löwenstein–Jensen medium. Murine macrophage (RAW264.7) viability and activity were evaluated through MTT and latex bead phagocytosis assays. Ultraviolet-wavelength spectrophotometry was used to analyze chemical structure changes. Glucomannan (0.05%–0.2%) significantly enhanced murine macrophage viability and activity. When glucomannan was combined with INH, the IC50 value was greater compared to INH only. Phagocytosis assays revealed heightened macrophage activity in the presence of 0.05% and 0.1% glucomannan. Importantly, glucomannan did not compromise INH efficacy or alter its chemical structure. This study underscores the potential of glucomannan, particularly with a lower molecular weight, as a promising enhancer of INH, boosting macrophage phagocytosis against INH-resistant Mtb. These findings challenge the assumptions about the impact of glucomannan on drug absorption and prompt potential reevaluation. While specific receptors for glucomannan in macrophage phagocytosis require further exploration, the complement receptors are proposed to be potential mediators.

Key words: Characteristic profile, glucomannan, isoniazid, macrophage phagocytosis, *Mycobacterium tuberculosis*

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INTRODUCTION

Isoniazid (INH) is recognized as a first-line antituberculosis (anti-TB) agent, acknowledged for its efficacy in eradicating *Mycobacterium tuberculosis* (Mtb) bacteria. INH exerts its antitubercular effects by impeding the synthesis of mycolic acids, pivotal components of the Mtb cell wall.[1,2]

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Enhancing the phagocytic ability of macrophages is crucial for preventing INH resistance in Mtb pathogenesis, as it facilitates more efficient engulfment and destruction of mycobacteria. This approach aims to augment the innate immune response,[3] promoting the clearance of INH-resistant strains by macrophages, which can be particularly important when antibiotic efficacy is compromised.

Macrophages recognize and eliminate pathogens and apoptotic cells, while Mtb can evade or exploit these cells for intracellular survival. Mtb produces protein and lipid effectors that regulate the functions of macrophages and their intracellular environment.[4,5] Effective phagocytosis requires mature macrophages and it leads to efficient Mtb clearance.[6,7] Several factors increasing receptor expression, enhancing cytokine signals, and modulating phagocytosis-related signaling pathways (the PI3K/Akt pathway and MAPK pathway), contribute to the heightened phagocytic capacity of mature macrophages.[8] These macrophages play a critical role against TB infection; they recognize pathogen-associated molecular patterns (PAMPs) present on the Mtb surface through various pattern recognition receptors (PRRs), including polysaccharides.[9,10]

Glucomannan, a polysaccharide with various biological effects, plays an important role in immune modulation.[11] Glucomannan demonstrates the ability to moderately activate macrophages and increase the synthesis of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha, enhancing phagocytosis against pathogens.[8] Glucomannan may help macrophages recognize Mtb through polysaccharide receptors. The aim of this study is to comprehensively characterize how glucomannan enhances INH efficacy and triggers macrophage viability and activity.

MATERIALS AND METHODS

The glucomannan (*Amorphophallus muelleri*) used in this study was obtained from PT. AMBICO, Surabaya, Indonesia, with concentrations ranging from 0.05% to 0.2%. INH was provided from PT. Mepro, Tangerang, Indonesia. In this study, several tests were conducted.

Animal handling for murine peritoneal macrophage phagocytosis assay

Four-day male mice (12 weeks old; 20–25 g) were obtained from the Veterinary Farma Center, Indonesian Ministry of Agriculture in Surabaya, Indonesia. The use of four mice was determined based on an optimized experimental setup, where four mice could yield approximately 1×10^7 peritoneal macrophages (equivalent to 40 replicates in 24-well plates). All mice were acclimatized in separate cages with 12 h of light-and-dark cycles and stable ventilation at room temperature (20°C–24°C) with 65% relative humidity. A standard chow diet was provided ad libitum for 14 days, and mice displaying signs of illness were excluded. To isolate peritoneal macrophages, mice were euthanized using neck dislocation methods.

Isoniazid sensitivity test

The INH sensitivity test assessed the inhibition of Mtb growth by INH and its combinations, using Mtb H37Rv ATCC 25618 cultured in Middlebrook 7H9 broth (OADC; BD, Difco)[12] and Löwenstein–Jensen medium (L3910, Sigma Aldrich) with INH and glucomannan, incubated for 8 weeks at 37°C in a Biosafety Level 3 incubator, with Mtb growth identified by brown, granular colonies through optical observation.

MTT assay for viability test

RAW264.7 murine macrophage cell lines were cultured in DMEM supplemented with L-glutamine, 10% FBS, 1% penicillin-streptomycin, and 0.5% amphotericin B for optimal growth. The MTT assay, using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, tested glucomannan concentrations of 0.05% and 0.1% to assess cell viability and metabolic activity. After treating cells with glucomannan and incubating, the MTT solution was added, and absorbance was measured to determine (%) cell viability and calculate the IC50, indicating the concentration causing a 50% reduction in viability, represented by a sigmoidal curve. The assay, conducted in triplicate for reliability, used Mann–Whitney *U* test statistical analysis to evaluate differences in viability between groups.

Characterization of isoniazid-glucomannan chemical structure changes using ultraviolet-wavelength spectrophotometer

For the preparation of INH and INH-glucomannan solutions, respective concentrations of 20 ppm, 40 ppm, 60 ppm, 80 ppm, and 100 ppm were achieved by dissolving and homogenizing the compounds. Spectra and absorbance measurements for each solution were conducted using an ultraviolet (UV)-wavelength spectrophotometer (PEAK, X-8200T, US). The measured spectral pattern was used to elucidate the characteristic changes of each concentration, providing insights into the molecular interactions within the solutions. The absorbance measurements were obtained at 279 nm.

Macrophage phagocytosis assay

The macrophage phagocytosis assay involved incubating murine peritoneal macrophages from 4-day male mice with 0.1 µm latex beads in RPMI 1640 medium (without phenol red, supplemented with L-glutamine and 10% FBS). After initial culture, macrophages were exposed to latex beads and varying glucomannan concentrations (0.05%, 0.1%, and 0.2%) to examine their effects on phagocytosis. Control groups included macrophages with only INH

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or glucomannan, creating six cohorts with five replicates each. After incubation, modified Giemsa staining on 1% collagen-coated slides enabled the quantification of phagocytosed beads under a microscope.

Statistical evaluation

Significance in this study was analyzed with GraphPad Prism 9.0 (San Diego, USA) using nonparametric Mann–Whitney *U* test statistical analysis. All results were considered statistically significant if $P < 0.05$.

RESULTS

Glucomannan increases viability and activity of murine cell macrophages

The MTT assay [Figure 1a] revealed that glucomannan (0.05%–0.2%) enhances RAW264.7 macrophage viability, with significant increases at 0.05% (132.37% ± 2.11%, $P = 0.0021$) and 0.1% (144.28% ± 2.21%, $P = 0.032$) over the baseline (0%, 100% viability). Adding 0.1% glucomannan raised the IC50 value for INH from 418.00 µg/ml to 468.80 µg/ml [Figure 1b, $P = 0.032$], indicating improved viability. In phagocytosis assays [Figure 1d], glucomannan increased macrophage engulfment of latex beads, especially in the late phagosome (phase-III) and phagolysosome (phase-IV) formation stages. Notably, 0.05% and 0.1% glucomannan increased phase-IV phagocytosis (58 ± 5, $P = 0.02$ and 77 ± 3, $P = 0.003$, respectively), compared to INH alone (39 ± 2; $P = 0.002$). Addition of 0.2% glucomannan resulted in a phagocytic pattern similar to controls (44 ± 6; $P = 0.003$), suggesting optimal glucomannan concentrations for enhanced macrophage function without affecting INH activity [Figure 1c and 1d].

Glucomannan did not alter isoniazid's efficacy and ultraviolet spectral profile

The visualization of the INH sensitivity test [Figure 2a] using Mtb strain H37RV shows that glucomannan did not affect INH efficacy in inhibiting bacterial growth (see GLU-INH compared with INH). Furthermore, glucomannan alone did not exert any inhibitory effect on Mtb growth (see GLU). Moreover, the mean UV spectral absorbance [Figure 2b] of the INH-glucomannan mixture showed a similar pattern to INH-only (see right panel), indicating that both INH (20, 40, 60, and 80 ppm) and INH-GLU 0.1% were strongly correlated ($r = 0.9994$) for their concentration and absorbance without further changing the chemical structure of each other. Figure 2c indicates INH-glucomannan ($r = 0.9998$) had a lower slope value and absorbance than INH only ($r = 0.9995$) in 40 ppm and 60 ppm.

DISCUSSION

In this study, we successfully demonstrated the potential of glucomannan as an enhancer of INH in promoting macrophage phagocytosis activity, providing new insights into the battle against INH-resistance Mtb infection. These

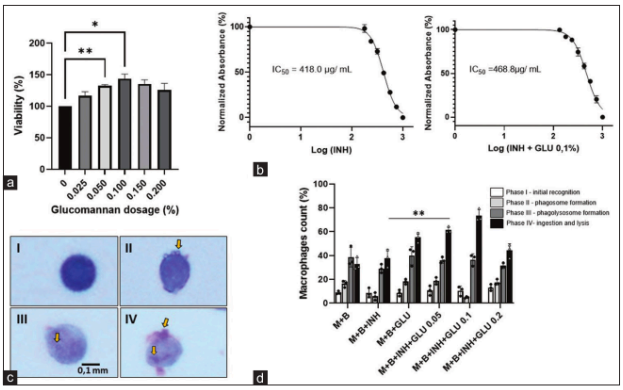

Figure 1: Glucomannan increases viability and activity of murine cell macrophages. Glucomannan concentrations ranging from 0.05% to 2% significantly increased the viability and phagocytic activity of murine macrophages, including both the macrophage cell line (RAW264.7) and peritoneal macrophages. (a) The MTT assay with the macrophage cell line (RAW264.7) demonstrates that glucomannan at 0.05% and 0.1% significantly elevated macrophage viability ($P < 0.05$), and (b) increased the IC50 (468.80 µg/ml) compared with INH alone (418.00 µg/ml). (d) The addition of 0.05%–0.1% glucomannan accelerated the end phase (Phase-IV) of macrophage phagocytic function. (c) A representative modified Giemsa stain of the four phagocytosis phases (Yellow arrows = position of latex beads, key differentiation in phase classification). *$0.05 \geq P > 0.01$, **$0.01 \geq P > 0.001$. ns = not significant. $n = 3$. INH: Isoniazid

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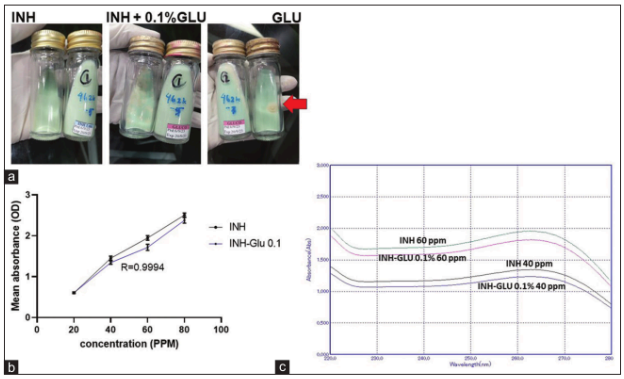

Figure 2: 0.1% glucomannan did not affect INH in chemical structure and its efficacy. (a) The INH-sensitivity test shows that glucomannan did not exhibit anti-mycobacterial activity. (b) The ultraviolet spectrophotometer analysis of mean absorbance between INH alone and INH-Glucomannan in different concentrations (20, 40, 60, and 80 ppm) revealed a similar range for both compounds, and both slopes exhibited a good correlation (*r*) between their concentration and absorbance. (c) A representative absorbance of INH and INH-GLU 0.1% in 40 ppm and 60 ppm. INH: Isoniazid

results challenge the conventional understanding of glucomannan's viscous nature. Despite previous studies implying that an excess of glucomannan in a "meal" dosage may hinder drug absorption due to glucomannan viscosity, this study suggests the potential for enhanced phagocytosis activity with a low concentration of glucomannan at 0.1% combined with INH in tablet form without altering the chemical structure and functionality of each component.

Macrophages act as "pathogen sensors" and are especially adept at phagocytosis. Activated macrophages (in phases III and IV) significantly increase their ability to destroy and break down intracellular bacteria. Latex beads are often used in experimental settings to mimic foreign particles or pathogens that macrophages encounter in the body.[13] When introduced to a sample containing macrophages, latex beads are recognized as foreign bodies by the macrophages' PRRs, as demonstrated by significantly higher levels in phases III and IV in our results. These receptors include scavenger receptors and toll-like receptors, among others. Similarly to the latex bead phagocytic pattern, the addition of glucomannan (0.05% and 0.1%) significantly induces phases III and IV. Moreover, the engulfment in phases III and IV was increased compared to the absence of glucomannan. This clearly indicates that low concentrations of glucomannan at 0.05% and 0.1% may improve the stability and solubility of INH, delivering it into Mtb, and increase the macrophage engulfment process, especially in phases III and IV. The finding in our manuscript potentially reevaluates the negative impact of glucomannan on drug absorption.[10,11]

In the UV spectrum, a lower difference in average absorption was observed for INH-GLU 0.1% compared to INH alone (specifically between 40 ppm and 60 ppm); these values still linearly produce a perfect correlation. This phenomenon may point us to the interaction between INH and GLU, which does not affect the response to UV light due to the similar UV spectral profiles between INH and INH-GLU. In addition, the lower linearity slope of INH-GLU than INH indicates that the UV absorption of INH-GLU is lower than that of INH. The single peak of INH-GLU indicates that the presence of glucomannan in INH does not affect the chromophore or auxochrome groups of INH, so it can still be detected by UV light[14,15]

To induce phagocytosis, specific receptors exclusively dedicated to recognizing glucomannan in murine macrophages have not been extensively documented. Macrophages typically employ various PRRs, such as scavenger receptors and toll-like receptors, to initiate the phagocytosis of foreign particles. We propose that the complement receptor, known for its distinct role in latex bead phagocytosis in macrophages, as observed in immortalized (HD11) cell lines, may function as a primary receptor, contributing to the acceleration of glucomannan-induced phagocytosis. However, further studies are needed to prove this hypothesis.

Interestingly, a higher concentration of glucomannan (0.2%) adversely affects phagocytosis ability, presenting an

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anomalous result that warrants further investigation into the diverse molecular weights of glucomannan and its mechanisms. Hypothetically, a higher glucomannan concentration (represented as 0.2% in this manuscript) might increase environmental viscosity, which could physically affect the engulfment process.[11,16] Taken together, glucomannan, most likely with a lower molecular weight, could potentially induce phagocytosis to eradicate INH-resistant Mtb.

CONCLUSION

This study highlights glucomannan's potential to enhance INH effectiveness in increasing macrophage phagocytosis, providing new insights for tackling INH-resistant Mtb infections. It suggests that combining a low concentration of glucomannan (0.1%) with INH could improve phagocytosis without changing the components' chemical structures, indicating a reevaluation of glucomannan's role in drug absorption. The study speculates that the complement receptor might facilitate glucomannan-induced phagocytosis, although further research is needed to confirm this. In addition, it finds that higher glucomannan concentrations (0.2%) negatively impact phagocytosis, underscoring the need to investigate how glucomannan's molecular weights affect phagocytic mechanisms. In summary, glucomannan, particularly with a lower molecular weight, shows potential in promoting phagocytosis and addressing infections resistant to INH in Mtb.

Institutional review board statement

This study was ethically approved by Preclinical Ethic Committee Gadjah Mada University, No. 00055/04/LPPT/XI/2023. Animal handling was executed following the standards set by the ARRIVE (Animal Research: Reporting of *In vivo* Experiments) guidelines.

Author contribution

Conceptualization: Bernadette Dian Novita, Widya Wasiyastuti, and Yudy Tjahjono; Methodology: Bernadette Dian Novita, Yudy Tjahjono, RM. Wuryanto Hadinugroho, and Sumi Wijaya; Formal analysis and investigation: Lisa Soegianto, RM. Wuryanto Hadinugroho, Imelda Theodora, Elisabeth T. W. Widoretno, Kevin Samsudin, and Alvin Julian; Writing – original draft preparation: Bernadette Dian Novita and Yudy Tjahjono; Writing – review and editing: Bernadette Dian Novita, Yudy Tjahjono, and Hendy Wijaya; Funding acquisition: Bernadette Dian Novita.

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Conflicts of interest

There are no conflicts of interest.

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