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Tryptophan and Its Derived Metabolites as Biomarkers for Tuberculosis Disease: A Systematic Review

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ABSTRACT

Feasible diagnostic assays are required to detect new TB cases and monitor treatment. This study aimed to evaluate evidence on Trp and its metabolites as proposed biomarkers for TB. Through specific keyword searches, we identified 170 relevant literature sources and included seven publications (from 2013 to 2023). The biomarker used in these studies were IDO activity, IDO-1 gene expression, and plasma IDO protein, measured using ELISA, LC-MS, UPLC, and transcriptional profiling. The studies encompassed a pediatric case-control and six studies involving adults, pregnant women with TB-HIV, and individuals with MDR-TB, active TB, and latent TB. The assessment of IDO activity and IDO protein level demonstrated promising performance in distinguishing active TB from controls and in evaluating treatment failure and recurrent cases to controls. Trp and its metabolites fulfilled nearly all of TPP criteria for detecting active TB. This study highlights the potential of utilizing host Trp and its metabolites as non-sputum-based biomarker for TB infection. ***DOI: 10.61186/ibj.4174***

Keywords: Biomarkers, Tryptophan, Tuberculosis

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INTRODUCTION

Tuberculosis, an ancient communicable disease caused by Mtb, is still a global public health concern[1,2]. Globally, 10.6 million people were infected with acid-fast bacilli, and 1.13 million deaths among HIV-negative individuals were attributed to these bacteria in 2022[3]. Early diagnosis is crucial for initiating TB treatment. However, only 8.7% of the net decrease in the incidence rate (2015-2022) has been achieved, which is still far from the WHO End TB Strategy target, that is of a 50% reduction in cases by 2025[3]. While TB is completely treatable[4], some patients encounter challenges such as recurrence, treatment failure, and death, which hinder global efforts to eradicate TB[5]. Monitoring treatment progress is vital, and utilizing non-sputum biologic markers plays a key role in evaluating treatment outcomes and distinguishing different forms of TB as well [6,7].

It is important that high-quality patient-centered diagnosis and care reach the End-TB target. The WHO has identified an urgent need for a non-sputum-based TB assay capable of detecting various forms of TB, as a tool to control the disease[8]. A study reported that the Trp pathway is highly regulated throughout TB infection spectrum. This observation made by employing high-resolution metabolomics with an unbiased approach to analyze the host metabolic pathways[9]. Trp, an essential amino acid, is catabolized through three main pathways in the host: the Kyn

List of Abbreviations:
AUC: area under the ROC curve; **HIV:** human immunodeficiency virus; **IDO:** indoleamine 2, 3-dioxygenase; **IPA:** indole propionic acid; **K/T ratio:** Kyn to Trp; **Kyn:** kynurenine; **LC-MS**: liquid chromatography-mass spectrometry; **MRD-TB:** multidrug-resistant tuberculosis; **MS:** mass spectrometry; **Mtb:** *Mycobacterium tuberculosis*; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **ROC:** receiver operator curve; **TB:** tuberculosis; **TPP:** target product profile; **Trp:** tryptophan; **UPLC:** ultraperformance liquid chromatography mass spectrometry; **WHO:** World Health Organization

pathway, serotonergic pathway, and gut-bacterial metabolism. The Kyn pathway allows the liver enzyme tryptophan 2,3-dioxygenase to metabolize about 95% of Trp into N-formylkynurenine[10,11], while IDO1 and IDO2 break down tryptophan in extrahepatic tissues. A small percentage (1-2%) of the consumed Trp follows the serotonergic pathway producing 5-hydroxy-tryptamine (serotonin, 5-hydroxytryptamine) in the gut (Trp hydroxylase 1) and in the brain (Trp hydroxylase 2)[11], which is then converted into melatonin. Gut bacteria also absorb this amino acid to generate biologically active metabolites that impact the host's physiology, by converting Trp into indole, skatole, indole-3-acetic acid, IPA, and indole-3-aldehyde[12-14]. This behavior underscores the significance of Trp and its metabolites in maintaining host homeostasis through its intricate metabolism and biological functions[13].

The upregulated Trp pathway in TB acts as an essential approach to identify disease biomarkers. An earlier study revealed that the activity of IDO, an interferon γ-inducible cytosolic enzyme that converts Trp to Kyn, can potentially serve as a biomarker for TB diagnosis[15]. The catabolism of Trp limits the growth of intracellular pathogens such as *Toxoplasma gondii*[16] and *Coxiella burnetii*[17]. Despite this, MTb has the ability to synthesize Trp, thereby counteracting the action of IDO without affecting its growth[18]. The breakdown of Trp may also serve as a mechanism for MTb to evade T cell response, leading to immune tolerance and the persistence of the bacteria in granulomas[19]. The increased catabolism of Trp in TB may be associated with not only the progression of active disease but also the pathology of the disease.

IPA is a metabolite that originates from Trp and is produced by gut microbiota and associated with TB pathogenesis[20]. Some gut bacteria known to produce IPA, including clostridia (*Clostridium sporogenes* and *Clostridium botulinum*) and *Peptostreptococcus anaerobius*. A study showed the anti-mycobacterial action of IPA both in vitro and in vivo, following a whole-cell fragment screening against Mtb[21]. This finding indicates a functional link between IPA-derived gut microbiota and TB. However, the precise role of this metabolite in disease susceptibility, progression, and severity has been yet to be established. Despite extensive research on potential biomarkers for TB diagnosis and treatment outcomes[22-26], the identification of highly sensitive and specific biological markers remains a significant challenge. None of these biomarkers have been applied in TB-endemic regions. This systematic review aims to compile recent literature on the potential role of Trp and its metabolites as biomarkers for TB.

MATERIALS AND METHODS

The study was conducted according to the PRISMA statement[27]. Figure 1 shows the PRISMA flowchart for this study.

Search strategy

On September 1, 2023, the author (NM) conducted a literature survey on the publications between January 1, 2013 and August 31, 2023 using the PubMed (National Library of Medicine of USA [NLM]) and Science Direct (Elsevier) databases. The author utilized the search terms 'tryptophan' in conjunction with 'TB' or 'pulmonary TB' or 'lung TB' and 'biomarker' or 'biologic marker'. The search was restricted to the studies conducted on humans, written in English and focused on biomarkers with diagnostic capabilities (sensitivity, specificity, and AUC). The author specifically abstracted studies that aimed to discover the diagnostic value of the Trp-derived biomarkers. The search and review process included literature containing possible combinations of the specified words.

Inclusion and exclusion criteria

The eligibility of the full texts articles was evaluated based on the inclusion criteria. These criteria encompassed: (a) original research that investigated Trp and its derived metabolite as biomarkers for TB, (b) articles published between January 1, 2013 and September 31, 2023, (c) articles written in English, (d) studies conducted on human subjects, and (e) peer-reviewed articles sourced from Scimago Quartiles. The exclusion criteria were taken into account when evaluating the eligibility of full-texts. These criteria included: (a) studies focused solely on sputum or urine samples, (b) retrospective studies, and (c) studies aimed to identify significantly elevated metabolites for TB biomarkers using metabolomics.

Selection of studies

Mendeley Desktop Reference Management System version 1.19.8 was utilized for compiling articles and eliminating duplicates. The article titles and abstracts were screened independently by two authors (ZZ and KH), among which the irrelevant titles were excluded. Full-texts were evaluated according to inclusion and exclusion criteria to determine the eligibility of the selected articles. The same authors independently assessed the articles, and those meeting the criteria were ultimately selected. In case of disagreements about eligibility, the third author (ZH) intervened to resolve the issue between the two independent researchers.

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Quality assessment

The quality of the included articles was evaluated by two researchers (ZZ and KH) using QUADAS, a tool designed for assessing the quality of studies on diagnostic accuracy in systematic reviews[28]. A checklist consisting of fourteen items with three response options (yes, no, and unclear) was utilized for this purpose. In cases of disagreement, a third author (ZH) intervened to resolve the discrepancies between the two independent researchers.

Data extraction and analysis

The objective of the study, methodology, and results from the included studies were extracted, summarized, and organized in a predefined extraction table (Table 1). This table included the following categories in columns: (a) year of publication, (b) author's name, (c) research topic, (d) biomarker, (e) sensitivity and specificity, (f) AUC, and (g) reference. These included studies conducted to differentiate between active TB and latent TB, active TB with HIV, active TB with HIV and HIV alone, MDR-TB and drug-sensitive TB, pediatric active TB and controls and also their response to treatment, along with active TB in pregnant patients with HIV and HIV patients. Sensitivity and specificity data were gathered from the included studies. The ROC was also used to evaluate the accuracy of biomarkers for various cut-off values.

RESULTS

Literature search

A total of 170 articles were recorded. After removing duplicates, the remaining 167 articles underwent a screening process to ensure congruity between their titles and abstracts. Of these 167 articles, seven were selected and evaluated based on the specific inclusion and exclusion criteria. Ultimately, these seven publications met the criteria and were included in this systematic review[9,29-34]. Figure 1 depicts the PRISMA statement flow chart, which outlines the steps of identification, screening, eligibility, and inclusion.

Characteristics of studies

A list of studies included in the analysis is summarized in Table 1. The articles selected for inclusion in the database search focused on Trp and its metabolites as potential TB biomarkers, with publication dates ranging from 2017 to 2023. These studies were conducted in various countries including India, China, South Africa, and the USA. According to the Journal Citation Ranking (JCR), six articles were published in Q1 journals, while one article was in a Q2 journal.

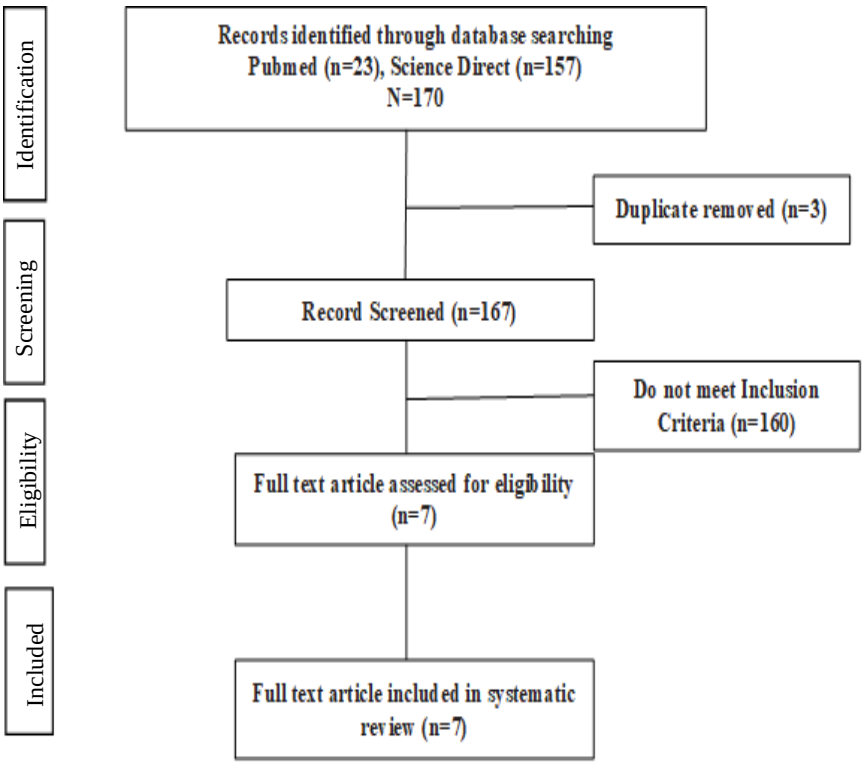

Fig. 1. PRISMA statement flow chart.

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Table 1. Characteristics of the included studies

Year	Ref.	Subject	Biomarker	Method used	Sens (%)/Spec (%)	AUC
2017	[29]	32 HIV-infected + TB patients, 70 HIV-infected control subjects, and 37 unmatched HIV-infected + pneumonia patients	IDO activity [Kyn:Trp ratio]	UPLC/MS	97/99	0.99
2019	[33]	18 DS-TB patients, 16 MDR-TB patients, 6 lung cancer patients, and 11 healthy sujects	IDO activity [Kyn:Trp ratio]	LC-MS	87.5/72.2 MDR-TB to DS-TB	0.88
2020	[9]	89 active TB patients, 57 control participants, including 20 LTBI Asymptomatic patients and 37 non-TB patients	- Trp:Kyn ratio Active TB to control	MS	99/42	0.92
2021	[31]	72 pregnant women with HIV + active TB to 117 pregnant women with HIV but without TB	IDO activity [Kyn:Trp ratio]	ELISA	94/90 Women with active TB to women without TB	0.95
2022	[34]	19 TB confirmed Pediatric patients under 15 years old	-Kynurenine abundance -Tryptophan abundance -K/T ratio -IDO-1 gene expression	UPLC Transcriptional profilling	-44/87 -41/94 -81/56 -33/75	-0.67 -0.60 -0.68 -0.46
2023	[32]	68 drug sensitive TB newly diagnosed to 108 control individuals	-Chitinase -IDO-1 -heme oxygenase-1 [HO-1]	ELISA	-100/83 -78/81 -52/64 Cases and controls -75/78 -93/97 -87/60 Failure of TB treatment to controls - 97/83 - 68/74 - 32/85 Recurrence to controls	-0.949 -0.842 -0.549 -0.816 -0.968 -0.660 -0.919 -0.735 -0.509

Ref.: reference; Sens: sensitivity; Spec: specificity; MS: mass spectrometry

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Patient's characteristic, biomarker used, and biomarker measurement method

Studies analyzed in this systematic review consisted of a pediatric case control study[34], as well as six studies involving adult TB-HIV co-infected patients[29,31], MDR-TB and drug-sensitive TB patients[33], active and latent TB[9,30,32], and active TB-HIV pregnant women[31]. The biomarker utilized in these studies was based on Trp and included measurement of IDO enzyme activity by assessing the Trp to Kyn ratio[9,29-31,33,34], IDO-1 gene expression[34], and plasma IDO protein itself[32]. The employed techniques were ELISA[30-32], LC-MS[9,33], UPLC[29,34], and transcriptional profiling of IDO[9,34].

Sensitivity, specificity and AUC of biomarkers

Table 2 represents the sensitivity, specificity, and AUC of the studies included. The majority of studies utilized the IDO enzyme activity measured by the ratio of converting Trp to Kyn. These studies demonstrated favorable sensitivity, specificity, and satisfying AUC of Kyn:Trp ratio (IDO activity) in distinguishing the active TB-HIV from HIV-infected patients (AUC = 0.99 and AUC = 0.93, respectively)[29,31], MDR-TB from drug-sensitive TB patients (AUC = 0.88)[33], active (AUC = 0.92) from latent TB (AUC = 0.92)[9,30], pregnant patients with HIV-infected from active TB (AUC = 0.95)[31], and pediatric TB patients (AUC = 0.68)[34]. The Kyn to Trp ratio (AUC = 0.68) was found to be superior to Kyn and Trp concentration alone (AUC = 0.67 and AUC = 0.60, respectively) in differentiating between active and latent TB in children[34]. Additionally, plasma IDO proteins alone exhibited high sensitivity and specificity in diagnosing TB compared to control subjects (AUC = 0.84), as well as in assessing TB treatment failure (AUC = 0.97) and TB recurrence in comparison to control subjects (AUC = 0.73)[32]. However, the IDO-1 gene expression demonstrated a low AUC in pediatric TB diagnosis and treatment response (AUC = 0.46)[34].

DISCUSSION

Studies have revealed the biomarkers that are candidate for active TB with acceptable diagnostic performance. These biomarkers are predominantly of host origin (including antibodies, cytokines, chemokines, and RNA signatures) and mycobacterial origin (Lipoarabino-mannan/LAM and Culture culture filtrate protein/CFP). They are tested using the patient's urine or blood sample[35]. The current systematic review examines the capability of Trp-based biomarkers in identifying active TB.

The operational characteristics of a diagnostic test suitable for primary care or at the point of care, are described in the high-priority TPPs by the WHO[36]. An ideal biomarker assay should be instrument-free or requires limited tools and has to be easily used with samples such as blood, urine, or breath. Non-DNA based biomarker assays are more likely to meet these operational characteristics and cost-effective TPPs compared to DNA-based assays[36-38].

We assessed the plasma K/T ratio as a blood-based diagnostic biomarker in different spectrums of TB disease. The studies included in this systematic review focused on pediatric TB patients, TB-HIV co-infection patients, pregnant patients with TB-HIV, MDR patients, active TB, latent TB, and healthy control subjects. The primary biomarker utilized was IDO enzyme activity, which was determined by the plasma K/T ratio and measured using ELISA, LC/MS, or UPLC/MS. The reported diagnostic performances exhibited acceptable sensitivity and specificity in distinguishing active TB

Table 2. Capability of Trp and its metabolite as disease biomarkers

Biomarker	Groups compared	Sens (%)/ Spec (%)	AUC	Ref.
IDO activity (Kyn:Trp ratio)	Active and latent TB	90/70	0.89	[30]
	Active TB and controls	99/42	0.92	[9]
	MDR-TB and DS-TB	87.5/72.2	0.88	[33]
	HIV + active TB and HIV + latent TB	90/80	0.93	[30]
	HIV-infected + TB patients and HIV-infected control subjects	97/99	0.99	[29]
	Pregnant women with active TB and pregnant HIV women without TB	94/90	0.95	[31]
	Pediatric TB patients and controls	81/56	0.68	[34]
IDO-1 protein level	Drug sensitive and controls	78/81	0.84	[32]
	Failure of TB treatment and controls	93/97	0.97	[32]
	TB recurrence and controls	68/74	0.73	[32]

Sens: sensitivity; Spec: specificity

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from controls. In diagnostic studies, AUC values above 0.90 were interpreted as a very good diagnostic performance of the test, and AUC values below 0.80 were considered acceptable. Six out of the total seven included studies revealed AUC > 0.80, which were capable in discriminating active TB from controls. Study on pediatric TB showed AUC < 0.70 of K/T ratio, which may be due to small sample size recruited.

Findings have suggested that the K/T ratio tends to be elevated in active TB patients at the time of diagnosis[39-41]. Additionally, HIV-infected patients displayed higher plasma K/T ratios compared to HIV-uninfected individuals, with the HIV viral reservoir affecting the plasma K/T ratio[42,43]. The plasma K/T ratio is a promising assay for TB diagnostic biomarkers following the WHO TPP guidelines[44]. It met 36 out of 37 TPP criteria for a non-sputum-based assay for detecting active pulmonary TB[44]. The IDO enzyme is induced by pro-inflammatory cytokines such as IFN-γ and TNF-α. Overexpression of IDO leads to peripheral immune tolerance to pathogens by depriving T cells of tryptophan, a crucial nutrient for T cell proliferation[45]. The catabolism of IDO produces toxic byproducts that accumulate in the microenvironment and induce regulatory T cells, which in turn suppress other immune cells[46,47]. Both MTb and HIV have been shown to induce IDO activity in vitro and in vivo[19,48,49]. However, unlike the host, MTb is capable of synthesizing its own tryptophan, which allows it to survive in a tryptophan-deficient granuloma[50].

ELISA assays offer a cost-effective and moderately high-throughput approach, which is suitable for peripheral laboratories and can be further automated. They require minimal sample volume and short processing time~~y~~. In contrast, mass spectrometry assay, a gold standard for measuring Kyn and Trp concentrations, is less common and more expensive, and requires specialized expertise, making them unsuitable for frontline disease diagnosis. The studies included herein demonstrated strong reproducibility and consistent results for the K/T ratio using both ELISA and MS methods.

This systematic review is robust, with a meticulously validated search strategy. The inclusion and exclusion criteria are well defined and easy to apply during screening. The quality assessment of all studies included in the review was conducted using the reputable and established tool, QUADAS. The absence of restrictions on patient groups in the inclusion criteria allowed for the examination of a commonly used biomarker in active and latent TB cases, as well as in both adults and children, irrespective of HIV or other comorbidities.

The limited time frame for the article searched from 2013 to 2023 was a limitation of this study, potentially excluding promising biological marker reported before. This review focused on Trp metabolites in TB, and the included studies exhibited the significant potential of Trp metabolites across various aspects of TB. Four articles examined active TB in comparison to healthy controls, two studies involved TB-HIV patients, and one focused on children. Future review should target specific cases, such as adult active TB, compared to healthy individuals and/or latent TB or TB-HIV compared to TB without HIV co-infection.

CONCLUSION

Research on biomarkers for TB is a highly active area of study; however, their overall impact have been somehow restricted. Challenges include investigating biomarkers in line with WHO TPPs, designing studies for specific cases, and conducting high-quality follow-up studies to improve TB detection and treatment monitoring. Trp and its metabolites have shown promise as a non-sputum-based test for detecting active pulmonary TB, meeting most TPP criteria. Further research is needed in larger and more specific patient groups with limited resources to highlight its potential in TB detection.

DECLARATIONS

Acknowledgments
No artificial intelligence was used in the production of this study.

Ethical approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions
NM: conceptualization, data curation, formal analysis, funding acquisition, writing; ZH: conceptualization, fnding acquisition, project administration, writing; KH: investigation, methodology, supervision, writing; ZZ: methodology, formal analysis, supervision, writing.

Data availability
All relevant data can be found within the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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