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REVIEW ARTICLE

Micronutrient Deficiency in Pulmonary Tuberculosis - Perspective on Hepatic Drug Metabolism and Pharmacokinetic Variability of First-line Anti-Tuberculosis Drugs: Special Reference to Fat-soluble Vitamins A, D, & E and Nutri-epigenetics

Jeyakumar Shanmugam Murugaiha[1,*]

[1]*Department of Clinical Pharmacology, ICMR-National Institute for Research in Tuberculosis (ICMR-NIRT), Chennai, 600031, Tamil Nadu, India*

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Abstract: The liver plays a crucial role in endogenous metabolic activity and homeostasis of macro and micronutrients. Further, it acts as a metabolic hub in mammals, where the ingested food-derived nutrients and xenobiotics or drugs are metabolized for utilization and/or excretion through its enzymatic and non-enzymatic machinery. Nutritional deficiency, one of the major public health problems, is associated with global disease burden, including pulmonary tuberculosis (PTB) caused by *Mycobacterium tuberculosis* (*Mtb*) infection. Though it is a curable and preventable infectious disease, millions of people succumb to death, and people in numbers larger than this are still suffering. This scenario is further complicated by the addition of new cases, disease recurrence, and the emergence of drug-resistant, all of which contribute to the spread of this epidemic. Though the manifestation of TB disease has multiple aetiologies, poor nutritional status and sub-optimal therapeutic concentrations of first-line anti-TB drugs are considered as potential contributors to its widespread prevalence. Among various factors, the pharmacokinetic variability of anti-TB drugs is one of the main causes for sub-optimal therapeutic drug concentration in TB patients, which is influenced by the host's genetic make-up and nutritional status, besides several others. However, the role of epigenetic changes in hepatic drug metabolic pathways and their transcript levels is largely unexplored. Therefore, in this review, an attempt has been made to understand the role of micronutrient deficiencies with special reference to fat-soluble vitamins, namely vitamin A, D, & E in pulmonary TB, their possible impact on epigenetic changes on the drug-metabolizing pathway genes, thus their expression levels and plausible influence on pharmacokinetic variability of anti-TB drugs, besides discussing the limitations and emerging potential opportunities. Eventually, this would help in developing the host-directed/personalized therapeutic strategies for the elimination of pulmonary tuberculosis (PTB).

Keywords: Cytochrome, liver, retinol, epigenetic, gene, enzyme, xenobiotic.

1. INTRODUCTION

Tuberculosis (TB) is the second leading cause of death from infectious diseases, caused by a bacterial agent, *Mycobacterium tuberculosis (Mtb)*. In 2019, more than 10 million new cases and around 1.5 million deaths due to tuberculosis had been recorded worldwide and majorly reported from the countries with limited resource settings, including socioeconomic status and healthcare/medical facilities. Particularly, in India, more than 2.4 million cases were reported in 2019, which account for 27% of the global TB cases [1, 2]. The manifestation of disease from *Mycobacterium tuberculosis (Mtb)* infection involves several closely linked and inter-independent factors associated with survival and elimination of pathogens, including the interplay between host immune system, other infections, health and nutritional status, to name a few. However, only 5-10% of infected individuals develop the disease associated with these influencing factors during their post-infective lifetime. Although the infection is transmittable (through aerosol), the disease is preventable, perhaps, curable [1, 2].

According to the current WHO-recommended guidelines to treat active, drug-susceptible TB involves a combination of multiple antibiotics/first-line drugs for about six months, under directly observed treatment short-course (DOTS). For the first two months (*i.e.*, intensive phase), the regimen consists of isoniazid (INH/H), rifampicin (RIF/R), pyrazinamide (PZA/Z), and ethambutol (EMB/E), followed by four months continuation- phase with isoniazid (INH/H) and rifampicin (RIF/R) [3]. Although DOTS has aimed at increasing the patients' adherence to the treatment with decreased duration, the achieved treatment success rate is 85%

*Address correspondence to this author at the Department of Clinical Pharmacology, ICMR-National Institute for Research in Tuberculosis (ICMR-NIRT), No.1 Sathiyamoorthy Road, Chetpet, Chennai, 600031, Tamil Nadu, India; E-mail: smjkumar@gmail.com

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for drug-sensitive TB globally [1, 4]. Thus, even after the completion of treatment, large numbers of patients either fail to respond or have relapses or develop a drug-resistant form of tuberculosis. Importantly, the patient response to treatment is highly complex and poorly understood, as it varies among patients and is influenced by several factors, including other co-morbid conditions [4]. Among several factors, pharmacokinetic variability of anti-TB drugs is considered as one of the key crucial factors contributing to treatment failure [5, 6]. Therefore, there is a need to understand the causes of treatment failure to improve the treatment outcome, which not only helps in eliminating tuberculosis but also prevents the emergence of drug-resistant tuberculosis, thus overall disease burden of this infectious disease.

Nutrients are the essential elements of any living organism. Unlike macro-nutrients, micro-nutrients requirements are relatively lower; however, their role in physiological functions is immense, spanning through embryogenesis to aging [7-9]. In addition, they play a protective role against various diseases (both infectious and non-communicable) by regulating numerous pathways and to name a few, cell proliferation, apoptosis, immune system, and inflammation [10-12]. Previously, several researchers have extensively reviewed these aspects with respect to the liver-gut axis and microbiome in various pathophysiological conditions and even in nutrient deficient and excessive conditions [13-16]. Therefore, these aspects are not covered here, and this review confines itself to micro-nutrient deficiency with special reference to fat-soluble vitamins, A, D, & E in pulmonary TB, their plausible role in bringing about epigenetic changes in hepatic drug-metabolizing pathways, thereby the expression of genes (enzymes and transporters) and the pharmacokinetic variability of anti-TB drugs. Besides limitations, the potential scope for understanding the drug metabolism and its pharmacokinetic variability associated with treatment outcome has also been discussed.

2. MICRONUTRIENT DEFICIENCY AND PULMONARY TB

Nutritional deficiency (both macro- and micro-nutrients) is one of the common and major public health problems of most developing countries, including India. Besides macronutrient deficiencies, the prevalence of micro-nutrient deficiencies, such as vitamin A, vitamin D, vitamin C, vitamin B12, iron, iodine, and zinc among the general Indian population have been reviewed previously [17-20]. Importantly, nutritional deficiencies are considered as one of the causative factors associated with global disease burden [21, 22]. Nutritional status, particularly micronutrient deficiencies and their association with the development of pulmonary TB and the bidirectional relationships, are well recognized in the context of communicable disease burden [23-25]. Low levels of vitamin A in pulmonary TB have been reported in South African children, besides no beneficial effect on the disease outcome with high vitamin A therapy [26]. Similarly, vitamin A deficiency has been reported in pulmonary TB among adults co-infected with HIV [27]. A cross-sectional study has reported low vitamin A levels among patients with pulmonary TB and asymptomatic HIV infection [28]. Furthermore, vitamin A deficiency has been reported in pulmonary TB patients of Indonesia, Ethiopia, and India [29-31]. Aibana *et al*., who have examined the vitamin A status and its association with TB, reported that vitamin A deficiency is a strong predictor of risk for TB incidence among household contacts of pulmonary TB patients [32]. Abundant literature and meta-analysis data have reported that vitamin D deficiency is associated with an increased risk of developing pulmonary TB [33-36].

Unlike vitamin A and D, vitamin E deficiency (due to insufficient intake through diet) is not a prevalent micro-nutrient deficiency in the general population; however, the deficiency occurs under several clinical and pathological conditions. In this regard, lower levels of circulating vitamin E levels have been reported in Ethiopian TB patients compared to healthy individuals [37]. Similarly, studies from India and Nepal have reported decreased levels of vitamin E among pulmonary TB patients compared to the healthy controls [38, 39a]. A recent study has found an inverse association between vitamin E status and increased risk for developing pulmonary TB among household contacts [39b]. A case-control study conducted in Korea has reported a higher prevalence of multiple vitamin deficiencies among pulmonary TB patients and found significantly lower plasma levels of fat- soluble vitamins A, D, and E, compared to the control subjects [40]. Earlier, Kant *et al*., who have reviewed the literature on nutrition and pulmonary TB have underscored the significance of various micronutrients (such as vitamin A, D, E, C, B6, calcium, zinc, iron, copper, and selenium), nutrient-drug interaction (particularly, rifampicin and isoniazid), and thus treatment outcome [41]. Further, the authors have outlined malnutrition as one of the risk factors for MTB infection; on the other hand, the infection can lead to nutritional deficiencies caused by loss of appetite, reduced food intake, malabsorption, and altered metabolism. Therefore, the authors have emphasized the importance of nutritional supplementation and periodical nutritional assessment of patients with pulmonary TB to bring down the illness (caused by infection and anti-TB drugs), faster recovery, and to improve overall treatment outcome [41]. Although undernutrition and micro-nutrient deficiencies have been reported among pulmonary TB patients from India by several investigators, still the studies are lacking in addressing the existence of multiple vitamin deficiencies in these patients [42-47]. Therefore, there is a need for studies establishing this aspect in Indian pulmonary TB patients, especially in view of the higher burden of nutritional deficiency and pulmonary TB in the Indian population. In a situation analysis report, Padmapriyadarsini *et al*. highlighted the detrimental effect of undernutrition in pulmonary TB, latent TB infection, and anti-TB drug-induced toxicity in the Indian context [48]. In addition, the authors urged various stakeholders to generate concrete evidence to understand the importance of nutrition and thus possible recommendations to extend nutritional support for the prevention and control of TB by various agencies to eliminate TB [48].

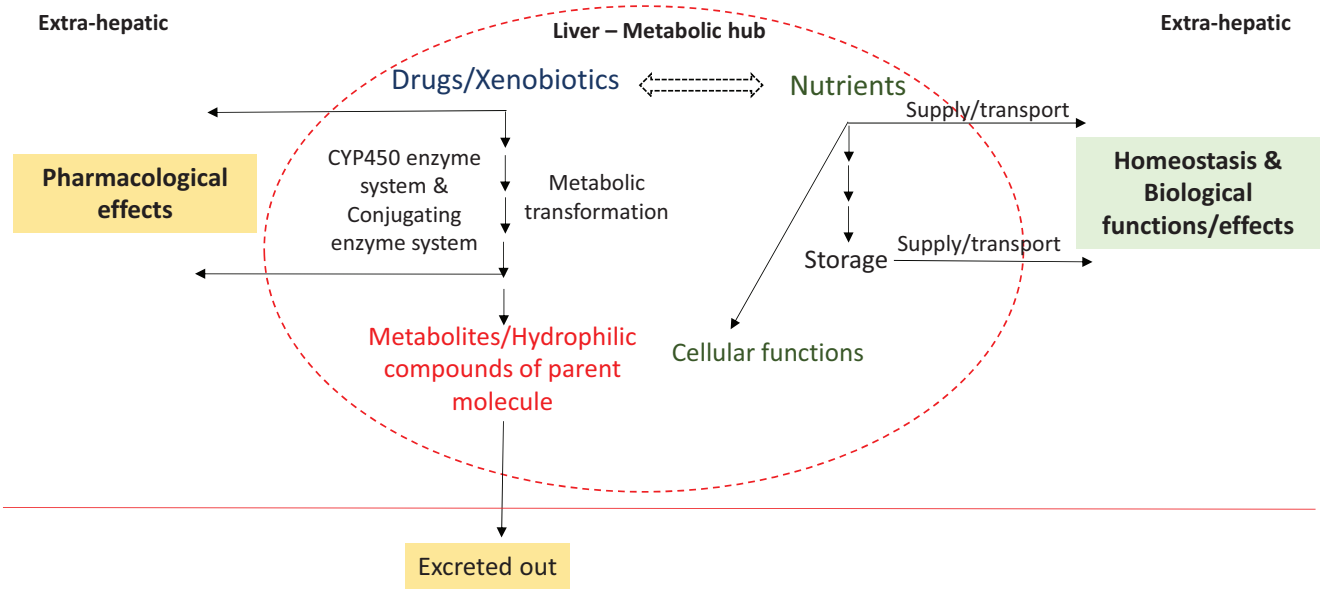

Fig. (1). Schematic summary of hepatic role in metabolism of drugs and nutrients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3. PHARMACOKINETICS VARIABILITY OF ANTI-TB DRUGS IN PULMONARY TUBERCULOSIS

Pharmacokinetic evaluation of anti-TB drugs provides the actual status of the drug administered, accounting for their absorption, distribution, metabolism, and excretion, thus helping in determining the steady-state level in circulation by adjusting the dose. Therefore, drug exposure is one of the key indicators of pharmacokinetic parameters, as defined by the area under the curve (AUC), in addition to maximum concentration (C_{max}) of the drug in circulation, which is associated with treatment outcome [49]. Previously, it has been reported that higher AUC is associated with increased efficacy, while the emergence of drug resistance is found with low C_{max} during anti-TB treatment [50]. However, the pharmacokinetic variability (*i.e.*, differences in drug exposure as defined by AUC) is influenced by several host factors, such as weight, age, pathophysiological conditions, nutritional status, and the genetic make-up of the individuals (A schematic summary is given in Fig. (**1**)). On the other hand, the drugs also have been documented to modify the nutritional status of the individuals and thus cause deficiency [51]. Way back, in 1982, Matsui and Rozovski underscored the effect of various drugs, including anti-TB drugs, such as INH and cycloserine, on the metabolism of nutritional factors, including vitamin B6, thus a secondary niacin deficiency [52]. Later, in 1985, Roe reported the bi-directional interaction and/or modifying the effects of nutrient and drug on each other, as the drugs can induce nutritional deficiency or toxicity, or the components of food, either macro- or micro-nutrients can alter their absorption, distribution, and exertion, therefore, their overall metabolism, thus therapeutic efficacy, in other words, the pharmacokinetic properties of the drugs [53]. Williams *et al*., who reviewed the impact of food on drug bioavailability and its clearance, have opined that the therapeutic efficacy or drug toxicity can be influenced by food-drug interactions [54, 55]. More than two decades ago, Zent and Smith, who studied the relationship between concomitant food intake and drug administration in patients with pulmonary TB, reported that the high carbohydrate diet results in 20% and 19% reduction of C_{max} and AUC8, respectively, for isoniazid, while 21% of Tm for rifampicin. Further, the investigators observed a 9% reduction of C_{max} for isoniazid with a high protein, high fat diet and thereby concluded that the food intake can reduce the bioavailability of rifampicin and isoniazid, thus treatment efficacy. Based on their findings, they arrived at the appropriate feeding time for optimal drug bioavailability [56]. A prospective randomized cross-over study that assessed the impact of food on first-line drugs reported a 16% and 15% reduction in the bioavailability of rifampicin and isoniazid, respectively, in drug-sensitive naïve TB patients, besides lowering the C_{max} for rifampicin, isoniazid, and pyrazinamide by 22%, 42%, and 10%, respectively concomitant with time delay in reaching C_{max}. Based on the data, the authors cautioned the risk of developing drug resistance due to poor efficacy resulting from decreased drug exposure due to interference with food [57].

4. LIVER - METABOLIC HUB FOR MICRONUTRIENTS AND DRUGS

The liver is the largest and key metabolic organ in the body and performs a plethora of essential metabolic functions in humans. In addition, the liver is the main site for the synthesis, secretion, degradation, and coupled inter-conversion and biotransformation of amino acids, carbohydrates, and lipids. Nevertheless, it is also involved in the storage,

transport, and cellular metabolism of micronutrients (both vitamins and minerals), hormones, and to some extent, filtration of blood. Besides these, the liver is the principal site for the detoxification of drugs and alcohol [58-62]. It has been estimated that, on the whole, all these activities may account for 25% of the body's total metabolic rate [63]. Hence, the liver is considered as a metabolic hub, as it connects various tissues, including the gut, brain, skeletal muscle, pancreas, and adipose tissue; thereby coordinating whole-body metabolism and homeostasis of bio-molecules, hormones, macro- and micro-nutrients. Besides, the metabolic removal of foreign molecules, particularly drugs (otherwise classified as xenobiotics) from the system, is an important activity of the liver, which confers pharmacological activity to some of the drugs [62]. A schematic summary is given in Fig. (**2**).

4.1. Micronutrient Metabolism

The liver plays a major role in the metabolism of vitamins, minerals, and trace elements (micronutrients). Liver reserves many essential nutrients, such as vitamins and minerals obtained through the hepatic portal blood supply. All the dietary fat-soluble vitamins after intestinal uptake are transported *via* the lymphatic system and distributed to peripheral tissues and the liver. Among the vitamins, vitamin A, vitamin D, vitamin B12, and vitamin K are reportedly stored in high amounts, while minerals such as copper and iron are found in higher concentrations in the liver. Although vitamin E is stored primarily in the adipose tissue, the liver plays a major role in vitamin E metabolism [64, 65]. It has been estimated that some of these stored nutrients are sufficient to meet the requirements for a year at least (*e.g.*, vitamin B12). Perhaps, the liver stores these micronutrients for its own metabolic functions or buffering purposes or for the supply to extrahepatic tissues on physiological demands or for the macronutrient metabolism [58-62, 64-67]. Among fat-soluble vitamins, 70-90% of vitamin A/retinol is stored in the stellate cells of the liver as lipid droplets. Further, the liver synthesizes and secretes the transporter protein for retinol, called retinol-binding protein (RBP) to supply retinol to the extra-hepatic tissues [68]. In addition, vitamin D binding protein (DBP), a member of the albumin gene family, is also synthesized by the liver [69]. Notably, alterations in the hepatic storage/levels of some of the key vitamins or minerals are known to adversely affect the liver functions, particularly macronutrient metabolism [66, 67]. Therefore, the normal function of the liver and metabolism of either macro- or micro-nutrients seem to be interlinked, tightly regulated, and comprehensively controlled.

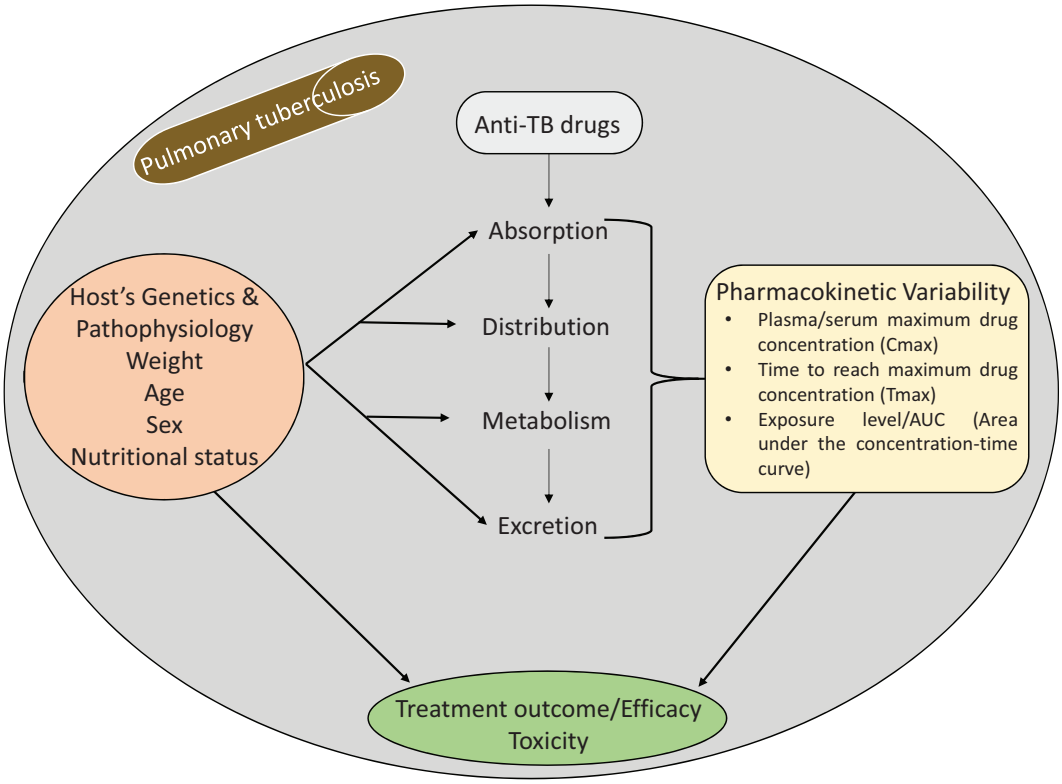

Fig. (2). Schematic summary of factors influencing drug metabolism and pharmacokinetic variability of drugs in pulmonary TB. The figure describes the role of several host factors in influencing the drug metabolism, which in turn the pharmacokinetic property of drugs and ultimately the treatment outcome/efficacy and toxicity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.2. Drug Metabolism

Elimination of drugs/xenobiotics from the body is a pivotal function of the liver, although the kidney and gut also play a role in this process. Importantly, during the process, several cascades of enzymatic pathway-mediated transformations of parent compounds occur, which ultimately make them more hydrophilic and ultimately get eliminated from the body. All these processes of drug metabolism are carried out by enzymes of phase I, phase II pathways, and transporter proteins of phase III pathway of various organs and, more importantly, liver, kidney, and gut. Most of the anti-TB drugs are metabolized by the Phase I & II pathway enzymes, which are mainly cytochrome P450 enzyme system and conjugating enzyme system, respectively [70, 71]. In humans, nearly thirty cytochrome P450 enzymes (CYP450) from the family 1-4, belonging to the cytochrome protein superfamily, are involved in the drug transformation/metabolism, and majorly six CYP450 enzymes of the family are involved in the oxidation of 90% drug metabolism, namely 2D6, 2C9, 1A2, 2C19, 2E1, and 3A4. In the phase II enzyme system, enzymatic conjugation of drug metabolites from the phase I pathway is carried out by UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), N-acetyltransferases (NATs), glutathione S-transferases (GSTs), *etc*. [70-73]. Previously, Devaleenal Daniel *et al*., extensively outlined the various confounding factors that influence the pharmacokinetic variability/intra-individual variation of anti-TB drugs and treatment outcome (though do not correlate with the therapeutic concentration of every individual undergoing treatment) [74]. Further, the authors underscored the challenges in understanding the pharmacokinetic variability of anti-TB drugs and the importance of pharmacogenomics in addressing these issues in treating patients with tuberculosis [74]. In a recent review, Almazroo *et al*. detailed the drug metabolism, its impact on liver health, and the role of several contributory factors influencing the drug metabolism, such as age, gender, drug-drug interactions, inflammatory mediators, gene polymorphism, *etc*. to a name few [71]. Thus, any changes in the drug metabolic pathway may alter the pharmacokinetics and pharmacodynamics properties of a drug.

5. ANTI-TB DRUG METABOLISM- A ROLE FOR NUTRI-EPIGENETICS?

In a recent review, Du Preez and Loots have exhaustively described the metabolism (novel metabolites) and mechanism of action of various first-line anti-TB drugs, using the pharmacometabonomic- approach. In addition, the authors have detailed various enzymatic and non-enzymatic pathways involved in the transformation of parent drug besides CYP450 enzymes in the host, that include some of the key enzymes, namely, N-acetyltransferase 2, amidase (INH), arylacetamide deacetylase (RIF), xanthine oxidase (PZA), alcohol dehydrogenase and aldehyde dehydrogenase (EMB) [75]. Importantly, the activities of these enzymes are regulated by several intrinsic (*e.g*., genetic and epigenetic) and extrinsic (*e.g*., diet and environment) factors and thus clearance of xenobiotics/drugs from the system. Among several drug-metabolizing enzymes, the pharmacogenomic analysis of N-acetyltransferase 2 has revealed the association between gene polymorphism and the rate of INH metabolism (as characterized by rapid, slow, and intermediate acetylators) and therefore, its influence on the INH concentration, thus pharmacokinetic variability of the INH. Although discordance exists with respect to phenotype and genotype relationship, the rate of INH metabolism (acetylator status) has been associated with the extent of bacterial sterilization and toxicity [76-79]. Similarly, some studies reported the pharmacokinetic variability of rifampicin, associated with nucleotide polymorphism in the solute carrier organic anion transporter family member 1B1 (*SLCO1B1* gene); a transporter protein involved in the hepatocellular uptake [80-83].

Unlike genetics, which deals with inherited changes in the nucleotide sequence of the DNA, epigenetics describes the heritable changes that alter the transcriptional regulation of genes without affecting the DNA sequence. However, it modifies the methylation and acetylation status of the DNA and histones, respectively, besides regulating the non-coding ribonucleic acid (such as micro RNA/miRNA and small interfering RNA/siRNA), and the changes are reversible [84, 85]. The role of epigenetics in cancer, cognition, cardiovascular disease, immunity, inflammation, and infection has been well described, besides its regulation by dietary nutrients, including fat-soluble vitamins [86-90]. Importantly, some of these vitamins are considered epi-nutrients or epigenetic modifiers [91]. However, studies on epigenetic changes and drug metabolic pathway enzymes and/or transporters by these fat-soluble vitamins are scanty in general and more so with respect to pulmonary TB. Among fat-soluble vitamins, vitamin A has an unusually wide range of biological functions and its active metabolite; retinoic acid, is known to exert most of the functions of vitamin A through its nuclear receptor superfamily, namely retinoic acid receptor (RAR) and retinoid X receptor (RXR), except for the role in vision, which is mediated by retinaldehyde. Retinoic acid is one of the potent transcriptional regulators through their nuclear hormone receptors (as homodimer or heterodimer or heterodimerize with other nuclear hormone receptor superfamily), binding to retinoic acid response elements (RARE) of the targeted genes in almost all cell types of mammalian species. Besides being the primary organ of vitamin A storage, the liver is a potent site for vitamin A action, as it expresses the nuclear hormone receptors (RAR, RXR), complete enzyme, and protein machinery to synthesis retinoic acid [92-94]. Literature reviews have highlighted the role of vitamin A and its nuclear receptors in mediating epigenetic modification during cell differentiation, proliferation, immunity, and carcinogenesis [95, 96].

Another fat-soluble vitamin, vitamin D, is known for its classical functions; bone metabolism and calcium homeostasis, while emerging studies have evidenced its role in non-skeletal functions, including cellular proliferation, differentiation, immune modulation, and hormonal regulation. Further, vitamin D-induced transcriptional regulation also involves the nuclear hormone receptor superfamily, vitamin D receptor (VDR). Notably, the VDR heterodimerises with

RXR under certain circumstances regulate the transcription of genes possessing vitamin D response elements (VDRE) [97, 98]. Recently, Wang *et al*. reported an association between methylation levels of various CYP450 genes (CYP24A1, CYP27A1, and CYP27B1) and serum vitamin D levels, which in turn determine TB risk and prognosis [99]. In a recent review, Wimalawansa highlighted the vitamin D deficiency-induced epigenetic changes and their associated dysregulation of various physiological functions [100]. In addition, vitamin E, another fat-soluble vitamin, is known for its potent antioxidant property. Unlike vitamin A and D, the metabolism of vitamin E is not well characterised; however, it is widely used in chemoprevention and inflammation-associated chronic diseases [101]. Importantly, recent studies have shown that vitamin E is an epigenetic modifier, which is evident from epigenetic regulation of miRNA and DNA methylation, thus gene expression [102-105]. Overall, many studies have shown that these fat-soluble vitamins are potent epigenetic modifiers, and therefore, it is plausible that the deficiency of these vitamins in pulmonary TB may dysregulate the transcription of the hepatic drug metabolic pathway enzymes and transporters (possibly even in kidney and gut), which in turn determines the pharmacokinetic property of anti-TB drugs (A schematic summary is given in Fig. (**3**)). However, to date, no such studies have been reported. Therefore, further research is needed to understand the association between drug metabolism and nutrients at least in pulmonary TB.

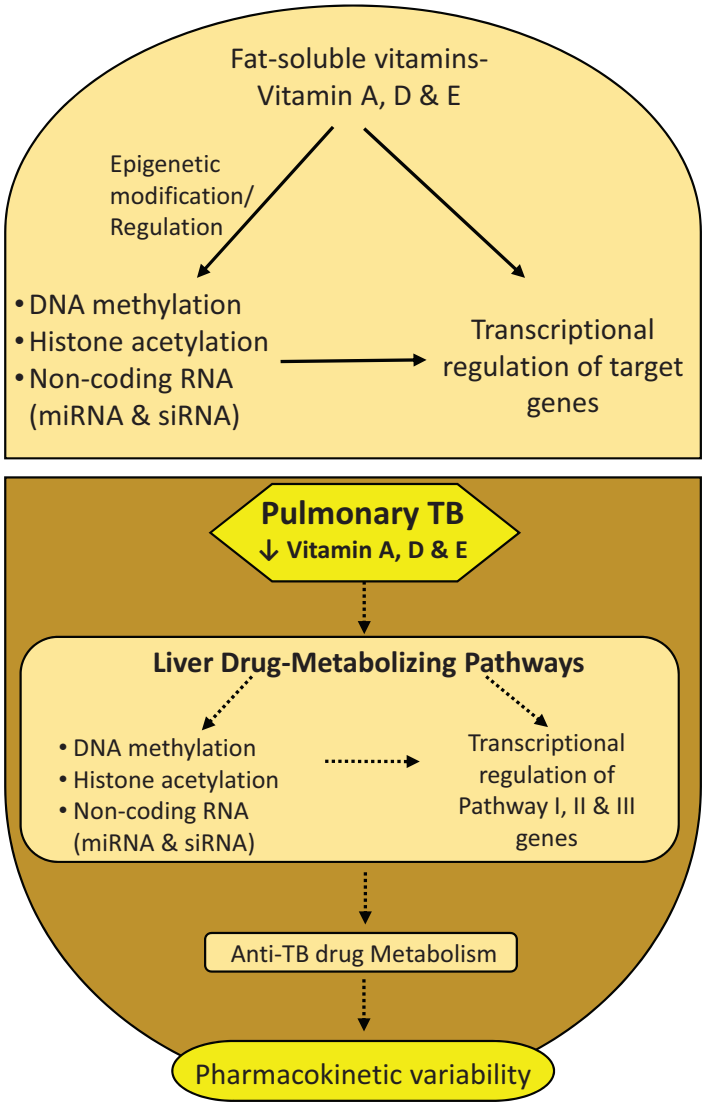

Fig. (3). Schematic summary of role of fat-soluble vitamins in epigenetic modification and transcriptional regulation.The upper part describes the role of vitamin A, D & E in epigenetic modification and transcriptional regulation of their targeted genes. The lower part depicts the plausible implications of vitamin A, D & E deficiency-mediated epigenetic modification and transcriptional regulation of hepatic drug-metabolizing pathways in pulmonary TB. Dotted arrows indicate that the role of these nutrients in hepatic drug metabolism in pulmonary TB is yet to be ascertained. miRNA - micro RNA and siRNA - small interfering RNA. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

6. SHORT-COMINGS AND OPPORTUNITIES

It is well established that both micronutrients and drugs are majorly metabolized by the liver; however, the bi-directional metabolic relationship between these two components is poorly understood due to high complexity. Importantly, so far, no studies have ever evaluated the role of these fat-soluble vitamins (Vitamin A, D & E) on the metabolism of anti-TB drugs and their pharmacokinetic variations, either at deficient or excessive conditions. For instance, the first-line anti-TB drug; ethambutol metabolism requires alcohol and aldehyde dehydrogenase (ADH and ALDH respectively) and these enzymes are also involved in the formation of retinoic acid from retinol after its conversion into retinaldehyde. In this scenario, whether the ethambutol ingestion would hamper the formation of retinoic acid and more so under vitamin A-deficient condition, thus the biological functions of vitamin A? Furthermore, retinoic acid is a substrate for CYP450 enzymes; CYP26A1 and CYP26B1, besides serving as a potential inducer of these enzymes. Notably, these enzymes are required to maintain the retinoic acid levels [106, 107]. However, it remains unanswered whether the anti-TB drugs have any influence on these enzymes, which in turn modulate the hepatic retinoic acid levels? Furthermore, retinoic acid is reported to modulate some of the hepatic drug transporters both at the gene and protein expression levels, that include sinusoidal solute carrier (SLC), influx transporters (namely organic anion transporting polypeptide (OATP 2B1, 1B1), organic cation transporter 1, organic anion transporter 2), canalicular breast cancer resistance protein (BCRP), and bile salt export pump (BSEP), through RXR:RAR in HepaRG cell lines, and human primary hepatocytes [108]. Thus, it appears that vitamin A and its metabolite, retinoic acid, not only modulate the phase I and II pathways enzymes, but phase III drug transporters as well, and therefore, possibly contribute to the variations in drug concentrations. Similarly, vitamin E has been shown to regulate genes involved in hepatic drug metabolism, including CYP3A through the pregnane X receptor (PXR), a nuclear hormone receptor superfamily [109]. More importantly, vitamin E and drug metabolizing pathways seem to interact with each other, as it has been shown that CYP4F2 is involved in the oxidation of vitamin E, while excessive vitamin E status is postulated to alter the drug metabolizing genes of phase I, II and III pathways [110, 111]. Therefore, one can speculate that the vitamin E deficiency in pulmonary TB may alter the metabolism of anti-TB drugs and their circulatory levels. However, several questions remain unanswered and need further research, at least from the perspective of hepatic drug metabolism and fat-soluble vitamins in pulmonary TB.

Although genetic variability and their influence on drug metabolism have been reported (at least limited to certain genes and anti-TB drugs), the epigenetic modification of drug metabolic pathway genes and hence the pharmacokinetic variability of anti-TB drugs in pulmonary TB is largely underexplored. Thus, it is imperative to assess the epigenetic changes occurring in drug-metabolizing pathway enzymes and transporters, their expression levels, and the association with fat-soluble vitamin status, along with the pharmacokinetics of anti-TB drugs in pulmonary TB. Unlike genetic variabilities, the epigenetic changes are reversible, and importantly, some of these vitamin levels are reported to be normalized at the end of the treatment in pulmonary TB. Thus, studies assessing the micronutrient status, epigenetic modification, expression profile of drug metabolizing enzymes and transporters, pharmacokinetics and therapeutic drug monitoring comprehensively from the stage of disease manifestation to the end of the treatment are the need of the hour, as this would address the interplay among nutrition, genetics, epigenetics of drug-metabolizing enzymes, therapeutic drug concentration and thus the treatment outcome. However, one of the key limitations to executing a study of this kind under clinical set-up, particularly for analysing the expression profile of various drug-metabolizing enzymes, is to find out the ideal surrogate cell type(s) preferably from a biological fluid, *i.e*., blood, so that the cells mimic the hepatic changes (due to vitamin deficiency and drug ingestion). Previously, in one of our experimental studies, we could find changes in the erythrocytes, similar to that of the liver for fatty acid composition during vitamin A-deficient conditions [112]. Thus, it is plausible that circulatory cell types may serve as a surrogate to study the drug metabolizing enzymes and/or transporters, at least at the transcriptional level. Nevertheless, the emerging technological advancement in the biological and computational sciences, including omics (epigenomics, transcriptomics, metabolomics, *etc*.), human organoids, *in-silico* models, artificial intelligence (AI)-based human cell models, and AI-based tools for predicting cell behaviour during different pathophysiological conditions would certainly help in overcoming some of the limitations in the current research and shed light on the intricate relationship among nutrients, drug metabolism, genetic, epigenetic and the treatment outcome, which in turn leads to the development of host-directed/specific or personalized treatment strategy for pulmonary TB, which will eventually and undoubtedly contribute to the TB elimination.

CONCLUSION

The metabolic transformation of both micronutrients and drugs occurs majorly in the liver, as it possesses complete enzyme and protein machinery to handle these two components. However, the understanding of their interaction in pulmonary TB is very poor. The emerging evidence demonstrates that among micro-nutrients, fat-soluble vitamins, vitamin A, D, and E are epi-nutrients or epigenetic modifiers and therefore, capable of modifying the hepatic drug-metabolizing enzyme and transporter pathway genes, thus their expression and drug metabolism, which in turn determines the pharmacokinetic property of drugs. However, so far, no studies have ever evaluated these aspects in pulmonary TB. Therefore, besides the host's genetics, there is a need for a comprehensive understanding of complex interactions of micro-nutrient status, epigenetic changes in hepatic drug metabolic pathways, their expression, drug metabolism, pharmacokinetic property, and their optimal therapeutic concentration in pulmonary TB. This would answer the role of micro-nutrients in hepatic drug metabolism, thus the therapeu-

tic concentration of drugs and its treatment outcome, at least in sub-sets of the population. Importantly, it is imperative to adapt newer technological advancements of the biological and computational sciences, including artificial intelligence-based technologies, to overcome some of the limitations in understanding the metabolism and interactions of drugs and micro-nutrients in pulmonary TB to achieve the goal of TB elimination.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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