Asian Pub. Corp.

www.asianpubs.org

REVIEW

Isoniazid: An Exploratory Review

Vandana Saini✉, Anju Goyal and Ajay Kumar

Asian Journal of Organic & Medicinal Chemistry

Volume: 7 Year: 2022
Issue: 1 Month: January–March
pp: 1–10
DOI: https://doi.org/10.14233/ajomc.2022.AJOMC-P373

Received: 15 February 2022
Accepted: 25 March 2022
Published: 5 April 2022

ABSTRACT

Isoniazid (INH) is one of the most successful tuberculosis medications in the market today. In particular, isoniazid is used as a prophylaxis medication to avoid resurgence of illness in those who have underlying *Mycobacterium tuberculosis* (MTB) infection. The mode of action of isoniazid is complicated and incorporates a number of distinct aspects in which various biomolecular routes are impacted, including mycolic acid production. Catalase-peroxidase (KatG) activates the prodrug isoniazid and enzymes such as β-ketoacyl ACP synthase (KasA) and enoyl acyl carrier protein (ACP) reductase target the active isoniazid products. Various genes in diverse biochemical networks and pathways are involved in the physiological mechanisms of isoniazid resistance. Isoniazid resistance is the most common of all clinical drug-resistant isolates, with incidence in some areas of up to 20 to 30%. In this review article, several existing components that may influence to the complexities of isoniazid function including mechanism of action, resistance mechanisms in MTB, along with their history, different synthetic procedures, uses, dosage forms, side effects, adverse drug reactions, physico-chemical characteristics, ADME properties, contraindications as well as future perspectives are discussed. Studies of pharmacokinetics have found that the cause of the drug mediated hepatotoxicity is possible by metabolism of isoniazid. Because of inter-individual heterogeneity of polymorphism that affect isoniazid metabolism rates, customized medicines may be required in various populations to prevent hepatotoxicity. The isoniazid multidrug combination treatment which would proved to be effective tuberculosis treatment in future. Further exploration is needed for better comprehension of pathogenesis mechanism of *Mycobacterium tuberculosis* (MTB) and drug resistance studies are required for building up better therapeutics and diagnostic against tuberculosis.

KEYWORDS

Mycobacterium tuberculosis, Drug resistance mechanisms, Isoniazid, Catalase-peroxidase, β-Ketoacyl ACP synthase.

INTRODUCTION

Tuberculosis (TB) is an atropical disorder of bacterial origin and it's far extra enormous than ever before and related to high ranges of death and distress [1]. Among 7.5 billion population of world, a large number of people have tuberculosis (TB) and everyday people dies from tuberculosis [2]. Tuberculosis is one of the most unusual infections due to *M. tuberculosis* (MTB). According to World Health Organization (WHO) about 75% of the world population is still uncovered to the tuberculosis pathogen. There are a range of factors that makes human being more vulnerable to infection with tuberculosis, In addition, smoking also increase the hazard of tuberculosis

Author affiliations:

Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

✉To whom correspondence to be addressed:

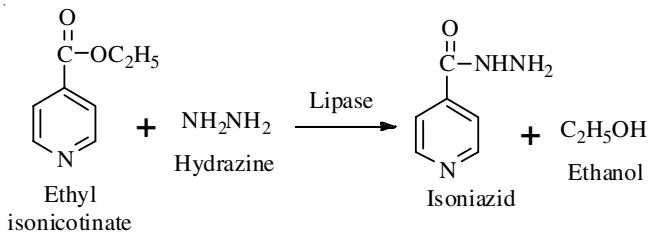
E-mail: vandana7027298741@gmail.com

Available online at: http://ajomc.asianpubs.org

[3]. In general tuberculosis chemotherapy is based on the management of isoniazid, rifampicin, pyrazinamide and ethambutol [4]. Pulmonary tuberculosis mainly results from MTB, which generally affect lungs, whereas extrapulmonary tuberculosis also be grow up form of *M. tuberculosis* and it damaged several body organs such as kidney, liver, tonsils, spleen, bones and brains [5]. For decades tuberculosis has afflicted mankind, but discovery of isoniazid (INH), incorporates a revolution in effective treatment of TB patients [6]. Multidrug-resistant tuberculosis (MDR-TB), in addition to resistant to isoniazid and rifampicin is becoming increasingly resistant to drugs [7]. Tuberculosis continues to be a significant global health epidemic, one of which is despite the implications, they have a huge effect on developed countries, availability for decades of highly successful care [8]. The drug resistant tuberculosis (DR-TB), multi drug resistant tuberculosis (MDR-TB), the challenges of drug resistant tuberculosis (XDR-TB) and completely drug-resistant tuberculosis (TDR-TB) are increasing worldwide [9]. The treatment of tuberculosis is boring, complicated and time-consuming [10]. Not withstanding the availability of an critical range of drug. Tuberculosis stays a tremendous global health threat [11]. Isoniazid also called isonicotinic acid hydrazide is the synthetic drug which was first recognized in 1912 and used as Anti-TB drug from 1952. The activity of isoniazid is selective as well as specific towards MTB complex and mycobacterial species [12]. In 1994, Heifets had shown that when INH is used at 0.02-0.2 µg/mL concentration range then it shows high susceptibility towards *M. bovis* and MTB complex. The excellent intracellular penetration and remarkable bactericidal property have made INH as most important antimicrobial agent [13]. Isonicotinic acid hydrazide (isoniazid, INH) originates to the family of first line antituberculosis. Drugs individual in medical practice more than 50 years [14]. Isoniazid and rifampicin are the most energetic drugs together to fight tuberculosis. Used along with different synergists in all instances of tuberculosis. The effect of these drugs contain good tolerance and low toxicity. To treat active tuberculosis, isoniazid is never used alone. Since resistance evolves rapidly. The improvement ranges of malaria parasites are also inhibited by isoniazid drug (*Plasmodium gallinaceum*) developed by mosquitoes. Isonicotinic acid and methanesulfonyl chloride are used to prepare isoniazid accompanied by a hydrazine reaction. It may not be using the form of acid chloride. Industrially used isoniazid is uneconomical [3]. In conjunction with other anti-TB agents, sufferers are allowed to administer a dose 300 mg of isoniazid daily for 9 months. But, there are many adverse side consequences related to isoniazid consisting of jaundice, liver toxicity, liver failure and hydralazine antihypertension. Because of those unfavourable effects, the isoniazid dosage perception is confined and while the sickness is handled with sub-therapeutic doses. There were no new anti-TB drugs delivered to the marketplace over the last 5 years [5]. In medicinal chemistry hydrazone and hydrazides have been commonly used.Various studies have revealed that hydrazide derivative possess significant activity against *Mycobacterium tuberculosis*. Such moiety being a key group for the antimycobacterial activity. Literally isoniazid also belongs from hydrazide.

During the metabolism of isoniazid hydrazine is formed, which causes hepatotoxicity through inflammation and may lead to death. In the case of anaerobic condition isoniazid is only active and growing on bacilli but not effective against non-replicating bacilli [7]. In medicinal chemistry isoniazid and its derivatives are nitrogen containing heterocycles moiety which have gained importance due to wide range of biological activites such as antimycobacterial, antibacterial, antivirus, antifungal, antitumor, antianalgesic, anticonvulsant activites [9]. Isoniazid drug mainly cause to increase the blood level of liver enzyme and hepatic toxicity appear as cellular necrosis and steatosis. However, the main metabolite of isoniazid drug is hydrazine.

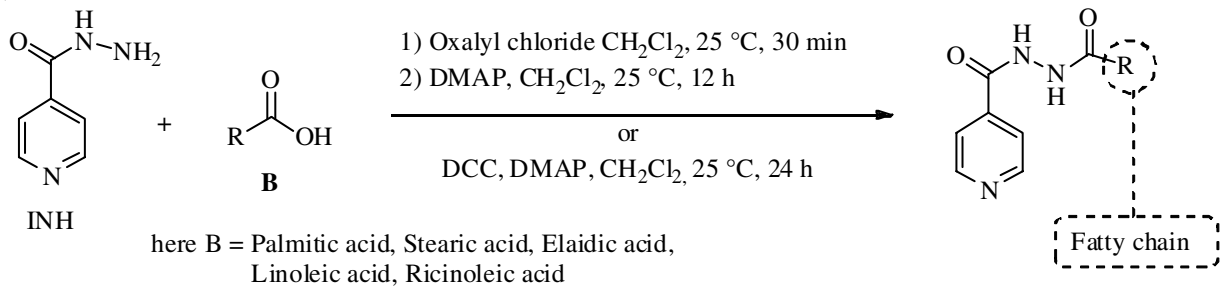
History of isoniazid: The isoniazid or isonicotinic acid hydrazide was first derived with the help of ethyl isonicotinate and hydrazine invented by Hans Meyer & Josef Melley in 1912 (**Scheme-I**). This drug was checked and approved by FDA and give the permision to treat the tuberculosis patients in 1952 with a particular inhibition activity towards *M. tuberculosis*. In 1954, morbidity were brought into clinical use after the tuberculosis-related mortality fell dramatically and decreased significantly. It soon because the pillar of tuberculosis treatment. In 1963, isoniazid was prescribed as monotherapy for use in prevention of tuberculosis. Due to the resistance of antimicrobials, isoniazid is frequently used with pyrazinamide rifampin, or combination therapy and both of these agents.



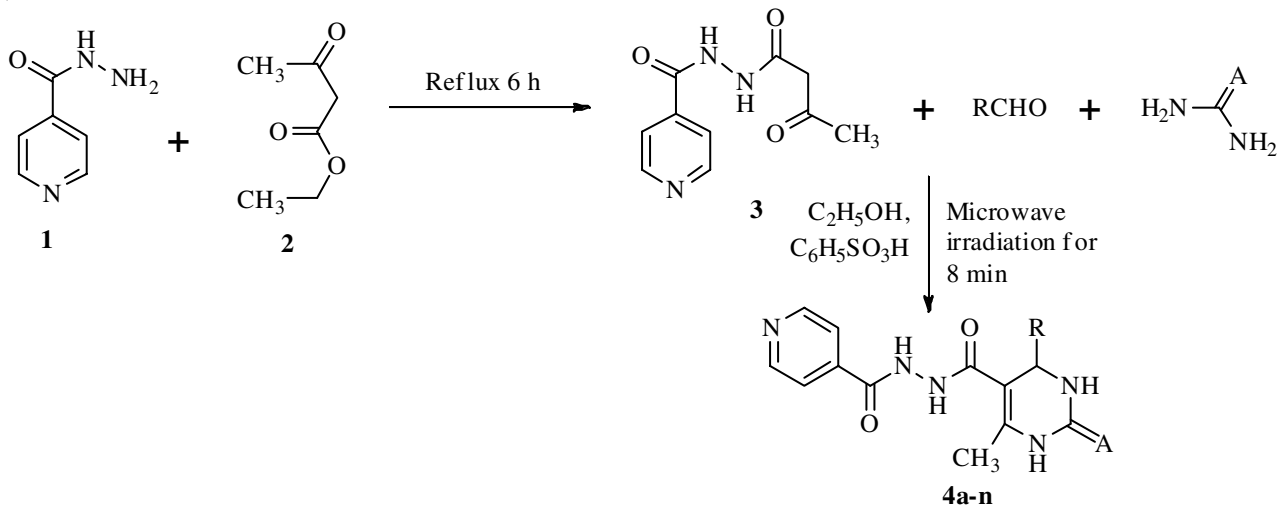
Scheme-I

Scheme-II involves reaction between INH and various derivatives of B as shown in reaction above in presence of various reagents. These derivatives were synthesized in 60-99% yield at room temperature. The ricinoleic acid derivatives whose precursor is ricinoleic acid is generally obtained from castor oil [1]. All the synthesized derivatives were purified by column chromatography and structure was evaluated by ^{13}C & ^{1}H NMR techniques. Most of these synthesized derivatives displayed MIC value of less than 6.25 µg/mL.

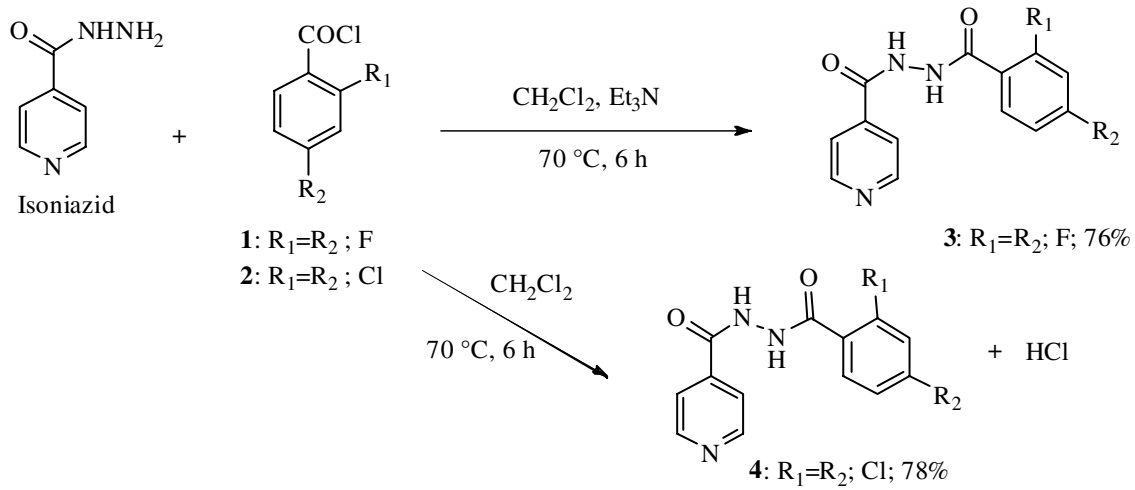
Scheme-III involves preparation of some novel isoniazid clubbed tetrahydropyrimidines that were obtained by reacting N′-acetoacetylisonicotinohydrazide with urea/thiourea and appropriate aldehyde in the presence of benzenesulphonic acid as catalyst. A green chemistry approach is utilized while performing this reaction. The synthesized derivatives were accessed for their antimycobacterial activity towards CIP and H37RV strain. The result indicated that **4l**, **4m**, **4n** had the most potent activity against standard drug rifampicin [15]. The compound 2,4-difluoro and 2,4-dichloro derivative of *N*-isonicotinoylbenzohydrazide hydrochloride *i.e.* (**3**) and (**4**) were synthesized as shown in **Scheme-IV**. The biological activities of these were also reported [16].



Scheme-II: Synthesis of isoniazid derivative containing fatty acid chain

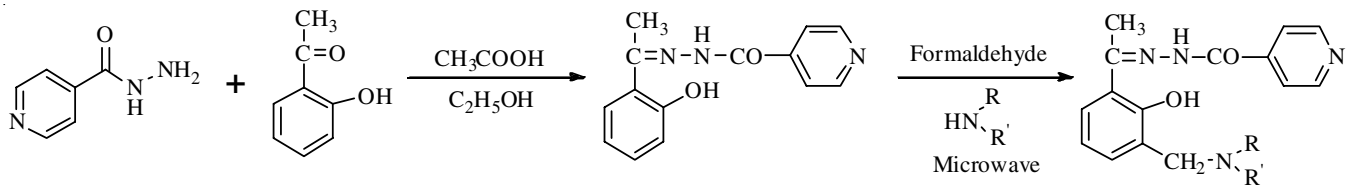


Scheme-III: Synthesis of isoniazid derivative having 1,2,3,4-tetrahydropyrimidine moiety



Scheme-IV: Synthesis of isoniazid derivative

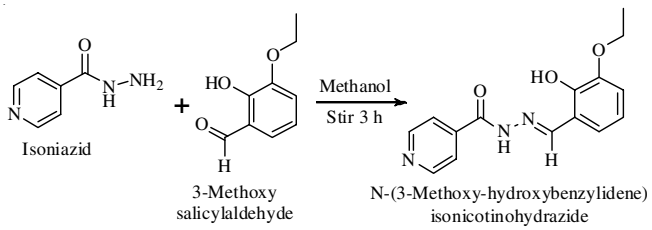
Scheme-V involves the reaction between isoniazid and O-hydroxy acetophenone to form hydrazones. The formaldehyde and different 2° amines were reacted with hydrazones to form Mannich bases. The compounds synthesized, were accessed against *M. tuberculosis* $H_{37}RV$ strain. Results indicated that compound **8** was found to be most potent (MIC =



Scheme-V: Synthesis of isoniazid derivative

0.56 µM) and also more potent than isoniazid (MIC of 2.04 µM) [17].

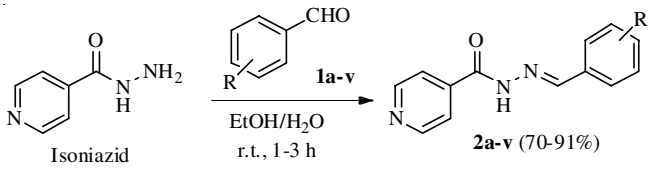
Scheme-VI involves the reaction between isoniazid and salicylaldehyde derivatives to form 3-methoxy-hydroxybenzylidene)isonicotinohydrazide. This product showed antimycobacterial activity of 4.0 µg/mL against MTB $H_{37}RV$ strain as compare to isoniazid [18].



Scheme-VI: Synthesis of isoniazid derivative

Scheme-VII involves the product formation by condensing isoniazid with equimolar ratio of fluoroisatin in presence of glacial acetic acid [19]. The product was purified by recrystallization and was shown to have good activity against MTB $H_{37}RV$ strain [20].

E-(Monosubstituted benzylidene)isonicotinohydrazides were synthesized by reaction between isoniazid and substituted benzaldehydes and accessed for their $H_{37}RV$ strain of MTB using Alamar blue susceptibility test (**Scheme-VIII**). Compounds **2f**, **2g**, **2j**, **2k** and **2q** have shown a remarkable activity (0.31-0.62 µg/mL) as compared to isoniazid and rifampicin as standard. These could be a decent new leads in the battle against multi-drug resistant tuberculosis which also need further exploration [21].

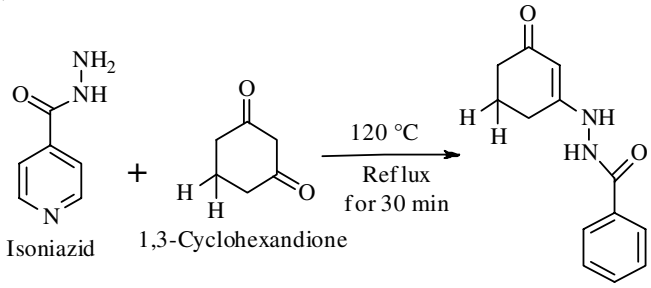


2a, R = H, **2b**, R = 2-Br, **2c**, R = 3-Br, **2d**, R = 4-Br, **2e**, R = 2-Cl, **2f**, R = 3-Cl, **2g**, R = 4-Cl, **2h**, R = 2-F, **2i**, R = 3-F, **2j**, R = 4-F, **2k**, R = 2-CN, **2l**, R = 3-CN, **2m**, R_3 = 4-CN, **2n**, R = 2-NO_2, **2o**, R = 3-NO_2, **2p**, R = 4-NO_2, **2q**, R = 2-OCH_3, **2r**, R = 3-OCH_3, **2s**, R = 4-OCH_3, **2t**, R = 2-OCH_2CH_3, **2u**, R = 3-OCH_2CH_3, **2v**, R = 3-OH

Scheme-VIII: Synthesis of isoniazid derivative

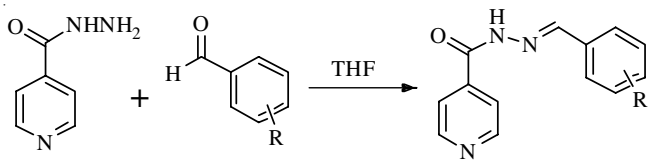
Scheme-IX involves the reaction between isoniazid and substituted benzaldehyde, acetophenones or benzophenone derivatives. The hydrazones were prepared and accessed against $H_{37}RV$ strain of MTB. Results displayed that compound **8** had the most potent activity with 0.56 µM, which is more than that of isoniazid [17].

Scheme-X involves reaction between isoniazid and 1,3-cyclohexandione. Reaction is subjected to reflux for 30 min at 120 ºC. All these derivatives had shown remarkable activity against $H_{37}RV$ strain of MTB as compared to standard drug [22].



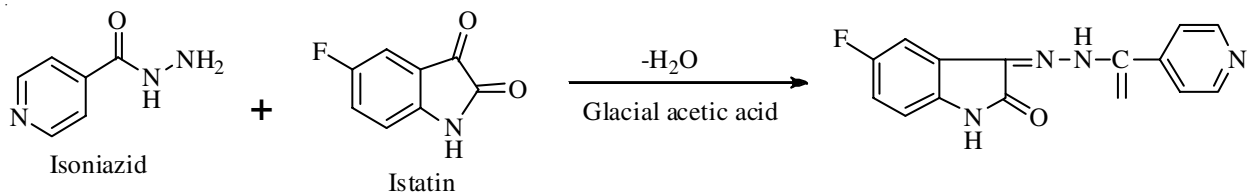
Scheme-X: Synthesis of isoniazid derivative

A reaction between benzaldehyde derivatives and isoniazid in presence of tetrahydrofuran was also carried out (**Scheme-XI**). The resulted compound was accessed for antimycobacterial activity against $H_{37}RV$ strain of MTB. Compound **11d** (*p*-nitro bearing derivative) displayed the excellent result with MIC 1.2 µg/mL as compared to standard isoniazid and rifampicin drug [23].

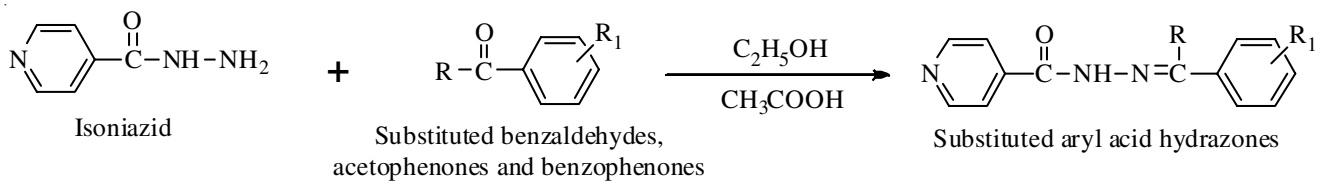


Scheme-XI: Synthesis of isoniazid derivative

Mechanism of isoniazid drug: The isoniazid inhibits the growth of bacteria for first 24 h [24,25]. The prodrug form of isoniazid engaged into cytoplasmic area of MTB by simple



Scheme-VII: Synthesis of isoniazid derivative



Scheme-IX: Synthesis of isoniazid derivative

passive diffusion [26] and inhibit the growth of bacteria in active phase. In other words, the MTB growth is not inhibited under anaerobic conditions or in stationary phase [27]. One of the most principle effects of isoniazid is the inhibition of mycolic acid synthesis of mycobacteria that results in loss of acid fastness [28] acids are long branched chain fatty acids that plays vital role for mycobacterias. Therefore, anti-TB drugs are mainly focused around inhibition of mycolic acid and treated it as vital targe [29]. The long multi-methyl chain of mycolic acid is essential for MTB virulence as well as offered resistance to antibiotic [30]. The electron microscopic studies has also revealed the toxic effect of isoniazid on cell surface of MTB [31,32].

Heazell [33], Winder and Collins [34] firstly proposed the inhibition of mycolic acid by isoniazid. After that Takayama *et al.* [35,36] reported the correlation between mycolic acid inhibition after isoniazid administration and MTB viability. Later on, Takayama *et al.* [37] again proposed the mycolic acid inhibition by blocking the fatty acid end chain followed by Davidson and Takayama [38], who indicated the inhibition of C_{24} and C_{26} fatty acid chain synthesis. The lethal effect of isoniazid was later proved by Vilcheze amd Jacobs [39]. Furthermore, it was also identified that acetyl transferases [40], acyl carrier protein reductase [41] and synthase [42] plays very important role in mycolic acid synthesis and these are very important target for anti-TB drugs [43].

The exact nature of isoniazid activity is still uncertain but earlier research showed that isoniazid under *in vitro* conditions is metabolized to several products, incorporation of which with MTB associated cell material leads to significant MTB toxicity. The metabolized product is generally yellow in colour [44], while in case of isoniazid resistant organisms, this yellow colour was not seen [29,45]. It was also evidenced that isoniazid also affects various lipid, protein, carbohydrate and nucleic acid pathways [46-49]. Furthermore, isoniazid is also responsible for NAD depletion [50] by activating NAD glycohydrolase or by exchange of nicotinamide from NAD [51]. Due to antibiotic prodrug, which is isoniazid inactive compound and metabolized in between the body and transform into an active form of drug and this procedure will be done by the presence of catalase-peroxidase enzyme followed by targeting of active isoniazid products towards enoyl acyl carrier protein (ACP) reductase and β-ketoacyl ACP synthase (KasA). The variability of isoniazid against *M. tuberculosis* is the result of its inhibition of mycolic acid synthesis, which is the basic component of the mycobacterium cell wall. The objective of isoniazid is InhA genetic material which is catalyzed in the presence of nicotinamide adenine dinucleotide (NADH), therefore isoniazid is activate through catalase peroxidase enzyme (KatG) and will connect to nicotinamide adenine dinucleotide to form an NAD-isoniazid compound, which blocks the interaction of nicotinamide adenine dinucleotide among InhA genetic material, consequently the action of InhA to make the fatty acids of mycolic acid and there will be no development of a mycobacterium cell wall [52].

Uses of isoniazid: Isoniazid is an efficacious medicine often used in tuberculosis treatment [53]. Isoniazid has been used in recent years not only to treat patients who have active tuberculosis but also for those with positive tuberculin reactivity [54]. It is used as an antibiotic that works by inhibiting the growth of bacteria [55]. In terms of tuberculosis prevention, 3 months of rifapentine plus isoniazid was successful for 9 months of isoniazid alone, with a higher treatment completion rate [56]. Second line drug are less effective and have higher side effect than first line antituberculosis drug [57].

Dosage

• The recommended dose of isoniazid is 300 mg per day for upto 9 months depending upon the disease condition.

• Active tuberculsosis is normally treated with 5 mg/kg for upto 300 mg per day or 15 mg/kg for upto 900 mg (upto 3 times a week).

• Isoniazid has better oral bioavailability in empty stomach [58] and if there is any abdominal discomfort, then it is recommended to administered it along with food or with non-aluminium containing antacid.

• Aluminium containing antacid is not recommended with isoniazid because aluminium binds to the isoniazid and prevents its intestinal absorption [59].

Furthermore pregnancy, breastfeeding and drug interactions ought to be reviewed prior to the administration of isoniazid [60,61].

Side effects: Hepatitis is one of the common infection developed during long period intake of isoniazid [62]. This occurs due to formation of acetyl hydrazine by liver as a result of metabolism of isoniazid. Isoniazid associated liver injury may occur at any stage of treatment [26,44,45]. In rare cases, due to progressive liver damage death may also occurs. The risk of hepatitis development is different for different age groups that is 1 out of 1000 patients for under 20 age groups, 3 out of 1000 patients for age between 20-34 years, 12 out of 1000 for age between 35-49 years, 23 out of 1000 patients for 50-64 age groups and 8 out of 1000 patients for over 65 years age group. The risk of developing is further synergized by consumption of alcohol [63-65]. For individuals, who completed the course of TB treatment may also develop little sort of liver injury and mortality rate among them is 23-58 out of 1 lakh patients. A large number of patients retrieved from isoniazid, induced hepatotoxicity after its discontinuance, although full reverting takes several weeks. The person under TB treatment must have blood liver tests from time to time and should immediately contact physician, if sign and symptoms could arise. These sign and symptoms includes abdominal discomfort, fever, fatigue, brownish urine, nausea, vomiting, appetite loss, painful joints, high blood sugar level, swollen lymph nodes, skin rashes, hypersensitivity reaction, gynecomastia and anaemia.

Damage to the nerves may also occurs due to continuous intake of isoniazid [66-68] and may cause tingling of feet and hands. Other rare side effects include inflammation in brain, atrophy, optic neuritis, Parkinson syndrome, psychosis and seizures.

Pyridoxine [69], a vitamin B_6 supplement decreases the risk of neural side effects in dose of 10-50 mg per day [70].

Adverse drug reaction: It has a number of adverse drug reaction, including neurological disability, hepatitis, gastrointestinal intolerance, allergic reactions, peripheral neuropathy and drug interactions [71].

Neurologic syndrome: The neurologic syndrome are the most well-known and well-documented adverse reaction of isoniazid. The most serious of these is peripheral neuropathy. The patient primary complains of numbness or tingling in the feet in the fully formed syndrome. The symptoms will decrease when the medicine is withdrawn at this point. Isoniazid can cause irritability, elation, agitation, insomnia and headache by stimulating the central nervous system. Laziness and sleepiness are also symptoms of central nervous system depression [72].

Gastrointestinal syndrome: Gastrointestinal symptoms such as nausea, vomiting, skin rashes, lupus-like syndrome and central neuropathy. During daily therapy, 12 patients developed gastrointestinal intolerance without significant hepatic function abnormalities, which were caused by rifampicin in 11 and isoniazid in 1 [73].

Other reactions: Even when used within therapeutic limits, isoniazid can cause liver damage. The formation of reactive oxidative species and other reactive metabolites by cytochrome P2E1 (CYP2E1) has been projected to play an vital role in isoniazid hepatotoxicity. Jaundice or yellowish discoloration of face, eyes and mucous membranes, pruritus, extreme abdominal pain, nausea or vomiting, weakness, severe fatigue, constant bleeding, skin rashes, generalized itching, swelling of the feet and/or legs, irregular and rapid weight gain in a short period of time, dark urine and light coloured stool are some of the signs of hepatotoxicity [74].

ADMET properties

Absorption: Number of studies have shown that isoniazid has low permeability to stomach region while it has high permeability to three intestinal region that are duodenum, jejunum and ileum [75,76]. The isoniazid drug is normally given orally, however if the patient is critically affected sick, it is possible to administered the drug i.m or i.v as a slow 5 min bolus of normal saline in 25 mL. It is available as a tablet (50, 100 and 300 mg) or a solution (50 mg/5 mL) for adults and 4-6 mg/kg with a standard 300mg dose is administered orally. On the other hand, it is possible to administer 8-12 mg/kg on one occasion 2 or 3 times in a weekly manner with a characteristic 900 mg dose. Isoniazid can be administered i.m and extremely injected right into a big muscle, generally the gluteus maximus, also 5 mg/kg (300 mg normally) every day or for 5 days in line with week or 15 mg/kg (900 mg classically) once, two or three times instances in line with week. Isoniazid can be administered by intramuscularly and extremely injected into a big muscle. When isoniazid can be taken with food, owing to the presence of fatty substances, they are reduced to hydrazine, so reducing the bio-availability and absorption of isoniazid [77-79]. When isoniazid is consumed it enters through the gastrointestinal tract where it absorb in small intestine and passed it to the liver with the help of hepatic portal system where it get metabolized.

Distribution: After absorption, isoniazid is spread into all over the body tissues, fluid and placenta as well. Isoniazid acts as prodrug, which get bio-transformed for activation and bactericidal function of isoniazid-nicotinamide adenine dinucleotide (INH-NAD) and adduct. This process takes place, inside MTB *via* KatG a catalase peroxidase in the presence of NADH. Studies have revealed that isoniazid in KatG knockout studies against MTB is poorly successful, showing the vital role of mycobacterial catalase peroxidase in bactericidal function of the antibiotic. Isoniazid will actively disperse through macrophage cells and Mtb cells due to its small size. KatG splits the hydrazine group of isoniazid into a free radical in MTB and then it oxidizes NADH to NAD^+. The host can also activate isoniazid by mammalian peroxidases, like human neutrophil myeloperoxidase and lactoperoxidase [80]. The average apparent delivery volumes for isoniazid was found nearly similar in 36 fast and 44 slow acetylators in kinetic experiments, provision of a possible 6 ± 1% body estimate 43 L (*i.e.* 0.61 × 70 L) weight for adult in medium size. Direct human studies found that large quantities of the medication are identified in the brain fluid, pleural effusions, saliva and faeces of both healthy and tuberculosis patients. This estimation has been obtained without plasma protein binding evidence, but as plasma proteins, it appears appropriate without improvement. Dog and rabbit studies have shown that isoniazid enters the placenta and excreted in breast milk at plasma like concentrations. New studies have revealed an outstanding penetration of isoniazid into dogs and sheep's sciatic nerves, implying that it can easily spread to human peripheral. The two main isoniazid metabolites acetylisoniazid and isonicotinuric acid, also are distributed in overall body water in the estimate of distribution volumes based on kinetic studies..

Metabolism: *N*-Acetyltransferase, which occur in the liver and the small intestine, is the major metabolic pathway of isoniazid [81-86]. There is a bimodal distribution of people who have acetylates quickly (approximately 40%) or slowly (approximately 60%) resulting in various half lives 45 to 110 min for fast and 2 to 4,5 h for sluggish metabolisms. Enzymes are also present. This behaviour indicates genetic variation. Hydrolysis glycine conjugation, hydrazone production and *N*-methylation reactions are used for other metabolites. None of the metabolites are working except monoacetylhydrazine, it means tuberculosis activity examine to be hepatotoxic [61]. The rate of acetylation are inherited and thus differ between patients. Some patients have a phenotype of fast acetylator, while others have a phenotype of sluggish acetylator. There is debate as to wether the latter exhibits hepatotoxicity manifestations more than the former, there are no variations in antimicrobial activity between these phenotypes [53].

Excretion: About 80% isoniazid metabolites {acetylisoniazid (AcINH), acetylhydrazine (AcHz), diacetyl-hydrazine (DiAcHz)} are excreted through urine. Some metabolites like as isonicotinic acid can be excreted as free acid and isonicotinyl glycine. When less than 10% of isoniazid is administered into the body with the help of mouth than it excreted by the way of feces and rest of the oral isoniazid excreted in breast milk. The effectiveness of removal owing to decreased or lack of function in patients with kidney or liver disorders has been reduced [6].

Toxicity: Studies of pharmacokinetics have found that the cause of the drug mediated hepatotoxicity is possible by metabolism of isoniazid [87-90]. Because of inter-individual heterogeneity of polymorphism that affect isoniazid metabolism rates, customized medicines may be required in various populations to prevent hepatotoxicity. In a clinical trial, a high oral

and injectable dosage of isoniazid of 7.5 mg/kg can be given to certain individuals with rapid acetylation without causing any adverse effects. In contrast, a lower dose of half the isoniazid level was used for the slow acetylators and thus the risk of hepatic injury was reduced. Patients clinical enhancement was evaluated using chest X-ray, population, sputum test and serum biochemistry testing. Because the frequency of quick acetylator genotypes varies among different ethnic groups such as a rapid acetylator genotype in Japanese populations is more frequent than in Caucasians, NAT2 genotyping is of further importance for the determination of the most effective isoniazid dosage.

Hepatotoxicity study of isoniazid: Hepatotoxicity is the most common adverse and dangerous side effect that can occur during tuberculosis treatment in adults as well as children [91-93]. Patients that are "late acetylators" who have elevated CYP2E1 levels are marginally more likely to develop isoniazid hepatotoxicity, but this increased risk is much too minimal to account for the idiosyncratic nature of isoniazid hepatotoxicity. Generally, isoniazid-induced hepatotoxicity shares certain characteristics, such as delayed onset, but there is considerable variation between patients [8]. Isoniazid is a hepatotoxic derivative of the drug hydrazine. Hydrazine and acetylhydrazine, two isoniazid metabolites, are mainly involved in the mechanism of isoniazid-induced hepatotoxicity [94]. Liver enzymes increase with isoniazid in 20% of the patients and 1-2% of the patients hepatotoxicity is a term to describe a condition in which the liver is damaged.

Resistance of isoniazid: Isoniazid-resistance is expanding all around the world and it represents a huge obstacle on the result of TB-treatment [95,96]. Ongoing precise reviews and *meta*-investigations have shown that isoniazid monoobstruction is related with diminished likelihood of effective standard therapy and an expanded risk of drug resistance [97]. Isoniazid resistance may not only diminish the productiveness of isoniazid preventive therapy but also increase the chances of MDR-TB [98] Isoniazid resistance can occur as the intracellular penetration of this medication is reduced [99]. There are two categories of main resistance mechanism for isoniazid, the first thing to prevent activation of isoniazid is to mutate katG.A drug activators respectively or to mutate their expression regulators. Second, isoniazid-nicotinamide adenine dinucleotide (INH-NAD) or ethionamide-nicotinamide adenine dinucleotide (ETH-NAD) adduct inhibition of InhA can be overcome by InhA or its promoter zone mutations [100]. Furthermore, transferring and expressing the wild-type *M. tuberculosis* katG gene into isoniazid resistant and katG mutant *M. tuberculosis* and mycobacterium smegmatis strains will improve isoniazid sensitivity [101]. Isoniazid resistance is the most common of all clinical drug-resistant isolates,with incidence in some areas of up to 20 to 30% [102]. There is,however, no evidence that isoniazid loss during pulmonary tuberculosis therapy causes the resistance [103].

Contraindications: Isoniazid doesn't give off an impression of being teratogenic and isn't contraindicated during breastfeeding or pregnancy, however pyridoxine supplement is suggested to patients with stable liver illness otherwise hepatic problem may be incremented. These patients ought to have more continuous monitoring from time to time [104].

Monitoring: In patients with pulmonarytuberculosis, month to month sputum examples are vital until there are two sequential negative reports to evaluate reaction to treatment. The prior measurement before starting isoniazid treatment includes aspartateaminotransferase (AST), alanineaminotransferase (ALT), bilirubin levels, alkaline phosphatase, creatinine and number of platelets. Custom observation of renal and hepatic function during treatment isn't required except if the sufferer has unusual standard expanded levels or at high risk of hepatotoxicity

Conclusion

The circumstances especially the worldwide resurgence of tuberculosis (TB) highlight the significance of the improvement of new anti-TB drugs and new conventions for therapeutic control of TB patients utilizing new anti-mycobacterial drugs. Additionally, it is difficult to exhibit advantage of new anti-TB drugs over prior drugs, since clinical preliminaries include multidrug combination treatment, which would proved to be effective tuberculosis treatment in future. Further exploration is needed for better comprehension of pathogenesis mechanism of MTB and numerous drug resistance issues for building up better therapeutics and diagnostic against TB. Concerning the advancement of new anti-TB drugs, the main focuses are of specific significance for example (i) development of better medications, which shows the long lasting antimycobacterial action *in vivo* and can be administered with long spans and therefore work with upgrade patient compliance and straightforwardly noticed way; (ii) development of novel compounds to battle MDR-TB is directly required; (iii) Destruction of MTB entities that cause reversion of TB by utilizing new lead class of anti-TB drugs, is extremely encouraging for anticipation of TB occurrence, since it will especially decrease the frequency of dynamic TB from people who are infected with MTB latently; (iv) Identification of new virulence genes of mycobacteria, which greatly promotes the development of new drug and (v) bioinformatics, Proteomics and QSAR studies by incorporating the knowledge for mycobacterial genomes may plays important role in the future drug discovery.

REFERENCES

1. M.O. Rodrigues, J.B. Cantos, C.R. D'Oca, K.L. Soares, T.S. Coelho, L.A. Piovesan, D. Russowsky, P.A. da Silva and M.G. D'Oca, Synthesis and Antimycobacterial Activity of Isoniazid Derivatives from Renewable Fatty Acids, *Bioorg. Med. Chem.*, **21**, 6910 (2013); https://doi.org/10.1016/j.bmc.2013.09.034
2. A. Tripathi, Y.F. Yadaf, D. Bilehal, S. Nayak and S.L. Gaonkar, A Review on Synthesis of Isoniazid Derivatives and their Biological Properties, *Int. J. Pharm. Res.*, **11**, 21 (2019).
3. F. Lentz, N. Reiling, A. Martins, J. Molnár and A. Hilgeroth, Discovery of Novel Enhancers of Isoniazid Toxicity in *Mycobacterium tuberculosis*, *Molecules*, **23**, 825 (2018); https://doi.org/10.3390/molecules23040825
4. E.M. Carvalho, Ph.D. Thesis, Metallo-Drugs as Nitric Oxide (NO) and/or Nitroxyl (HNO) Donors: Development of New Agents and Investigation of Anticancer, Antihypertensive and Antituberculosis Activities. Université Paul Sabatier, Toulouse, France (2020).
5. B. Saifullah, P.E.L. Arulselvan, M.E. Zowalaty, S. Fakurazi, T.J. Webster, B.M. Geilich and M.Z. Hussein, Development of a Biocompatible Nanodelivery System for Tuberculosis Drugs based on Isoniazid-Mg/Al Layered Double Hydroxide, *Int. J. Nanomedicine*, **9**, 4749 (2014); https://doi.org/10.2147/IJN.S63608

6. E.R. Erwin, A.P. Addison, S.F. John, O.A. Olaleye and R.C. Rosell, Pharmacokinetics of Isoniazid: The Good, the Bad, and the Alternatives, *Tuberculosis*, **116**, S66 (2019); https://doi.org/10.1016/j.tube.2019.04.012
7. D.G. Ghiano, A. Recio-Balsells, A. Bortolotti, L.A. Defelipe, A. Turjanski, H.R. Morbidoni and G.R. Labadie, New One-Pot Synthesis of Anti-tuberculosis Compounds Inspired on Isoniazid, *Eur. J. Med. Chem.*, **208**, 112699 (2020); https://doi.org/10.1016/j.ejmech.2020.112699
8. H.M. Hassan, H.L. Guo, B.A. Yousef, Z. Luyong and J. Zhenzhou, Hepatotoxicity Mechanisms of Isoniazid: A Mini-Review, *J. Appl. Toxicol.*, **35**, 1427 (2015); https://doi.org/10.1002/jat.3175
9. Y.Q. Hu, S. Zhang, F. Zhao, C. Gao, L.S. Feng, Z.S. Lv, Z. Xu and X. Wu, Isoniazid Derivatives and their Anti-Tubercular Activity, *Eur. J. Med. Chem.*, **133**, 255 (2017); https://doi.org/10.1016/j.ejmech.2017.04.002
10. W.M. Eldehna, M. Fares, M.M. Abdel-Aziz and H.A. Abdel-Aziz, Design, Synthesis and Antitubercular Activity of Certain Nicotinic Acid Hydrazides, *Molecules*, **20**, 8800 (2015); https://doi.org/10.3390/molecules20058800
11. A. Rani, M.D. Johansen, F. Roquet-Banères, L. Kremer, P. Awolade, O. Ebenezer, P. Singh, Sumanjit and V. Kumar, Design and Synthesis of 4-Aminoquinoline-Isoindoline-dione-Isoniazid Triads as Potential Anti-Mycobacterials, *Bioorg. Med. Chem. Lett.*, **30**, 127576 (2020); https://doi.org/10.1016/j.bmcl.2020.127576
12. E.H. Robitzek and I.J. Selikoff, Hydrazine Derivatives of Isonicotinic Acid (Rimifon Marsilid) in the Treatment of Active Progressive Caseous Pneumonic Tuberculosis; A Preliminary Report, *Am. Rev. Tuberc.*, **65**, 402 (1952); https://doi.org/10.1164/art.1952.65.4.402
13. J.B. Whitney and M.A. Wainberg, Isoniazid, The Frontline of Resistance in *Mycobacterium tuberculosis*, *McGill J. Med.*, **6**, 114 (2002); https://doi.org/10.26443/mjm.v6i2.686
14. E. Vavrikova, S. Polanc, M. Kocevar, J. Kosmrlj, K. Horvati, S. Bosze, J. Stolarikova, A. Imramovsky and J. Vinsova, New Series of Isoniazid Hydrazones Linked with Electron-Withdrawing Substituents, *Eur. J. Med. Chem.*, **46**, 5902 (2011); https://doi.org/10.1016/j.ejmech.2011.09.054
15. K. Elumalai, M.A. Ali, M. Elumalai, K. Eluri and S. Srinivasan, Novel Isoniazid Cyclocondensed 1,2,3,4-Tetrahydropyrimidine Derivatives for Treating Infectious Disease: A Synthesis and *in vitro* Biological Evaluation, *J. Acute Dis.*, **2**, 316 (2013); https://doi.org/10.1016/S2221-6189(13)60151-1
16. F F.P. Silva Jr., J. Ellena, M.L. Ferreira, Y.P. Mascarenhas, M.V.N. de Souza, T.R.A. Vasconcelos, J.L. Wardell and S.M.S.V. Wardell, Experimental and Theoretical Structure Characterization of Two Isoniazid Derivatives: 2,4-Difluoro-N′-isonicotinoylbenzohydrazide and 2,4-Dichloro-N′-isonicotinoylbenzohydrazide Hydrochloride, *J. Mol. Struct.*, **788**, 63 (2006); https://doi.org/10.1016/j.molstruc.2005.11.023
17. D. Sriram, P. Yogeeswari and K. Madhu, Synthesis and *in vitro* and *in vivo* Antimycobacterial Activity of Isonicotinoyl Hydrazones, *Bioorg. Med. Chem. Lett.*, **15**, 4502 (2005); https://doi.org/10.1016/j.bmcl.2005.07.011
18. E. Pahlavani, H. Kargar and N. Sepehri Rad, A Study on Antitubercular and Antimicrobial Activity of Isoniazid Derivative, *Zahedan J. Res. Med. Sci.*, **17**, 1 (2015); https://doi.org/10.17795/zjrms1010
19. D. Sriram, P. Yogeeswari and G. Gopal, Synthesis, Anti-HIV and Antitubercular Activities of Lamivudine Prodrugs, *Eur. J. Med. Chem.*, **40**, 1373 (2005); https://doi.org/10.1016/j.ejmech.2005.07.006
20. S. Haider, Z.S. Saify, N. Mushtaq, Z.M.M.-N. Tabinda, A. Arain, S.M. Ghufran Saeed and S. Ashraf, Synthesis of 4-(1-pyrrolidinyl)piperidine Derivatives as Anti-bacterial and Anti-fungal Agents, *World J. Pharm. Res.*, **3**, 11 (2014).
21. M.C.S. Lourenço, M.L. Ferreira, M.V.N. de Souza, M.A. Peralta, T.R.A. Vasconcelos and M.G.M.O. Henriques, Synthesis and Anti-Mycobacterial Activity of (E)-N′-(Monosubstituted-benzylidene)-isonicotinohydrazide Derivatives, *Eur. J. Med. Chem.*, **43**, 1344 (2008); https://doi.org/10.1016/j.ejmech.2007.08.003
22. H.H. Jardosh and M.P. Patel, Design and Synthesis of Biquinolone–Isoniazid Hybrids as a New Class of Antitubercular and Antimicrobial Agents, *Eur. J. Med. Chem.*, **65**, 348 (2013); https://doi.org/10.1016/j.ejmech.2013.05.003
23. M.C.S. Lourenço, M.V.N. Souza, A.C. Pinheiro, M.L. Ferreira, R.S.B. Gonçalves, T.C.M. Nogueira and M.A. Peralta, Evaluation of Anti-Tubercular Activity of Nicotinic and Isoniazid Analogues, *ARKIVOC*, 181 (2007); https://doi.org/10.3998/ark.5550190.0008.f18
24. G. Middlebrook, Sterilization of *Tubercle bacilli* by Isonicotinic Acid Hydrazide and the Incidence of Variants Resistant to the Drug *in vitro*, *Am. Rev. Tuberc.*, **65**, 765 (1952).
25. D.A. Mitchison and J.B. Selkon, The Bactericidal Activities of Antituberculous Drugs, *Am. Rev. Tubercul. Pulmon. Dis.*, **74**, 109 (1956).
26. F. Bardou, C. Raynaud, C. Ramos, M.A. Laneelle and G. Lanrelle, Mechanism of Isoniazid Uptake in *Mycobacterium tuberculosis*, *Microbiology*, **144**, 2539 (1998); https://doi.org/10.1099/00221287-144-9-2539
27. W.B. Schaefer, The Effect of Isoniazid on Growing and Resting *Tubercle bacilli*, *Am. Rev. Tuberc.*, **69**, 125 (1954); https://doi.org/10.1164/art.1954.69.1.125
28. N.K. Dutta and P.C. Karakousis, Eds.: D.L. Mayers, J.D. Sobel, M. Ouellette, K.S. Kaye and D. Marchaim, Mechanisms of Action and Resistance of the Antimycobacterial Agents, In: Antimicrobial Drug Resistance: Mechanisms of Drug Resistance, Cham: Springer International Publishing, vol. 1, pp. 359-383 (2017).
29. R.A. Slayden and C.E. Barry III, The Genetics and Biochemistry of Isoniazid Resistance in *Mycobacterium tuberculosis*, *Microbes Infect.*, **2**, 659 (2000); https://doi.org/10.1016/S1286-4579(00)00359-2
30. T.W. Lin, M.M. Melgar, D. Kurth, S.J. Swamidass, J. Purdon, T. Tseng, G. Gago, P. Baldi, H. Gramajo and S.C. Tsai, Structure-based Inhibitor Design of AccD5, An Essential Acyl-CoA Carboxylase Carboxyl-transferase Domain of *Mycobacterium tuberculosis*, *Proc. Natl. Acad. Sci. USA*, **103**, 3072 (2006); https://doi.org/10.1073/pnas.0510580103
31. K. Takayama, L. Wang and R.S. Merkal, Scanning Electron Microscopy of the H37Ra Strain of *Mycobacterium tuberculosis* Exposed to Isoniazid, *Antimicrob. Agents Chemother.*, **4**, 62 (1973); https://doi.org/10.1128/AAC.4.1.62
32. J. Testart, S. Chamoun and P. Jouanneau, *Chirurgie memoires de l'Acad. de chirurgie*, **103**, 305 (1977).
33. M.A. Heazell, Is ATP an Inhibitory Neurotransmitter in the Rat Stomach, *Br. J. Pharmacol.*, **55**, 285 (1975).
34. F.G. Winder and P.B. Collins, Inhibition by Isoniazid of Synthesis of Mycolic Acids in *Mycobacterium tuberculosis*, *J. Gen. Microbiol.*, **63**, 41 (1970); https://doi.org/10.1099/00221287-63-1-41
35. K. Takayama, E.L. Armstrong and H.L. David, Restoration of Mycolate Synthetase Activity in *Mycobacterium tuberculosis* Exposed to Isoniazid, *Am. Rev. Respir. Dis.*, **110**, 43 (1974); https://doi.org/10.1164/arrd.1974.110.1.43
36. K. Takayama, L. Wang and H.L. David, Effect of Isoniazid on the *in vivo* Mycolic Acid Synthesis, Cell Growth, and Viability of *Mycobacterium tuberculosis*, *Antimicrob. Agents Chemother.*, **2**, 29 (1972); https://doi.org/10.1128/AAC.2.1.29
37. K. Takayama, A.D. Keith and W. Snipes, Effect of Isoniazid on the Protoplasmic Viscosity in *Mycobacterium tuberculosis*, *Antimicrob. Agents Chemother.*, **7**, 22 (1975); https://doi.org/10.1128/AAC.7.1.22
38. L.A. Davidson and K. Takayama, Isoniazid Inhibition of the Synthesis of Monounsaturated Long-Chain Fatty Acids in *Mycobacterium tuberculosis* H37Ra, *Antimicrob. Agents Chemother.*, **16**, 104 (1979); https://doi.org/10.1128/AAC.16.1.104
39. C. Vilcheze and W.R. Jacobs, Isolation and Analysis of *Mycobacterium tuberculosis* Mycolic Acids, *Curr. Protoc. Microbiol.*, **5**, 10A (2007); https://doi.org/10.1002/9780471729259.mc10a03s05
40. S. Bhakta, G.S. Besra, A.M. Upton, T. Parish, C. Sholto-Douglas-Vernon, K.J. Gibson, S. Knutton, S. Gordon, R.P. DaSilva, M.C. Anderton and E. Sim, Arylamine *N*-Acetyltransferase is Required for Synthesis of Mycolic Acids and Complex Lipids in *Mycobacterium bovis* BCG and Represents a Novel Drug Target, *J. Exp. Med.*, **199**, 1191 (2004); https://doi.org/10.1084/jem.20031956

41. A. Banerjee, E. Dubnau, A. Quemard, V. Balasubramanian, K.S. Um, T. Wilson, D. Collins, G. De Lisle and W.R. Jacobs Jr., inhA, a Gene Encoding a Target for Isoniazid and Ethionamide in *Mycobacterium tuberculosis*, *Science*, **263**, 227 (1994); https://doi.org/10.1126/science.8284673
42. K. Mdluli, R.A. Slayden, Y. Zhu, S. Ramaswamy, X. Pan, D. Mead, D.D. Crane, J.M. Musser and C.E. Barry III, Inhibition of a *Mycobacterium tuberculosis* β-Ketoacyl ACP Synthase by Isoniazid, *Science*, **280**, 1607 (1998); https://doi.org/10.1126/science.280.5369.1607
43. W. Bauer, The Adolescent Who has Lost a Significant Other, *IMJ III Med. J.*, **148**, 614 (1975).
44. J. Youatt, The Metabolism of Isoniazid and Other Hydrazides by Mycobactria, *Aust. J. Exp. Biol. Med. Sci.*, **38**, 245 (1960); https://doi.org/10.1038/icb.1960.25
45. J. Youatt, Pigments Produced by Mycobacteria on Exposure to Isoniazid, *Aust. J. Exp. Biol. Med. Sci.*, **39**, 93 (1961); https://doi.org/10.1038/icb.1961.9
46. P.R. Gangadharam, F.M. Harold and W.B. Schaefer, Selective Inhibition of Nucleic Acid Synthesis in *Mycobacterium tuberculosis* by Isoniazid, *Nature*, **198**, 712 (1963); https://doi.org/10.1038/198712b0
47. M. Tsukamura and S. Tsukamura, The Fate of ^{35}S-Labeled Mycobacterium in Animal Body. Modification of ^{35}S Distribution in Mouse Organs by Adjuvant, *Jpn. J. Tuberc.*, **11**, 14 (1964).
48. I. Chopra and P. Brennan, Molecular Action of Anti-Mycobacterial Agents, *Tuber. Lung Dis.*, **78**, 89 (1998); https://doi.org/10.1016/S0962-8479(98)80001-4
49. F.G. Winder and S.A. Rooney, The Effects of Isoniazid on the Carbohydrates of *Mycobacterium tuberculosis* BCG, *Biochem. J.*, **117**, 355 (1970); https://doi.org/10.1042/bj1170355
50. A. Bekierkunst, Nicotinamide-Adenine Dinucleotide in *Tubercle bacilli* Exposed to Isoniazid, *Science*, **152**, 525 (1966); https://doi.org/10.1126/science.152.3721.525
51. L.J. Zatman, N.O. Kaplan, S.P. Colowick and M.M. Ciotti, The isolation and Properties of the Isonicotinic Acid Hydrazide Analogue of Diphosphopyridine Nucleotide, *J. Biol. Chem.*, **209**, 467 (1954); https://doi.org/10.1016/S0021-9258(18)65474-2
52. J. Adewuyi, H. Ibrahim and A.O. Oyewale, Synthesis, Characterization and Antimicrobial Evaluation of Novel 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives with Two Oxadiazole Rings, **4**, 9 (2011).
53. A.M. El-Brashy and S.M. El-Ashry, Colorimetric and Titrimetric Assay of Isoniazid, *J. Pharm. Biomed. Anal.*, **10**, 421 (1992); https://doi.org/10.1016/0731-7085(92)80060-Z
54. J.R. Mitchell, H.J. Zimmerman, K.G. Ishak, U.P. Thorgeirsson, J.A. Timbrell, W.R. Snodgrass and S.D. Nelson, Isoniazid Liver Injury: Clinical Spectrum, Pathology and Probable Pathogenesis, *Ann. Intern. Med.*, **84**, 181 (1976); https://doi.org/10.7326/0003-4819-84-2-181
55. U. Aleem, R. Shah, N. Khan and M. Suliman, Hepatoprotective Effects of Honey in Isoniazid (INH) Induced Hepatotoxicity in Rabbits, *Prof. Med. J.*, **25**, 1587 (2018); https://doi.org/10.29309/TPMJ/18.4635
56. T.R. Sterling, M.E. Villarino, A.S. Borisov, N. Shang, F. Gordin, E. Bliven-Sizemore, J. Hackman, C.D. Hamilton, D. Menzies, A. Kerrigan, S.E. Weis, M. Weiner, D. Wing, M.B. Conde, L. Bozeman, C.R. Horsburgh Jr. and R.E. Chaisson, Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection, *N. Engl. J. Med.*, **365**, 2155 (2011); https://doi.org/10.1056/NEJMoa1104875
57. H.F. Chambers, J. Turner, G.F. Schecter, M. Kawamura and P.C. Hopewell, *Antimicrob. Agents Chemother.*, **49**, 2816 (2005); https://doi.org/10.1128/AAC.49.7.2816-2821.2005
58. A.K. Kumar, V. Chandrasekaran, A.K. Kumar, M. Kawaskar, J. Lavanya, S. Swaminathan and G. Ramachandran, Food Significantly Reduces Plasma Concentrations of First-Line Anti-tuberculosis Drugs, *Indian J. Med. Res.*, **145**, 530 (2017); https://doi.org/10.4103/ijmr.IJMR_552_15
59. A. Hurwitz and D.L. Schlozman, Effects of Antacids on Gastrointestinal Absorption of Isoniazid in Rat and Man, *Am. Rev. Respir. Dis.*, **109**, 41 (1974).
60. N. Singh, A. Golani, Z. Patel and A. Maitra, Transfer of Isoniazid from Circulation to Breast Milk in Lactating Women on Chronic Therapy for Tuberculosis, *Br. J. Clin. Pharmacol.*, **65**, 418 (2008); https://doi.org/10.1111/j.1365-2125.2007.03061.x
61. K. Gausi, L. Wiesner, J. Norman, C.L. Wallis, C. Onyango-Makumbi, T. Chipato, D.W. Haas, R. Browning, N. Chakhtoura, G. Montepiedra, L. Aaron, K. McCarthy, S. Bradford, T. Vhembo, L. Stranix-Chibanda, G.R. Masheto, A. Violari, B.T. Mmbaga, L. Aurpibul, R. Bhosale, N. Nevrekhar, V. Rouzier, E. Kabugho, M. Mutambanengwe, V. Chanaiwa, M. Nyati, T. Mhembere, F. Tongprasert, A. Hesseling, K. Shin, B. Zimmer, D. Costello, P. Jean-Philippe, T.R. Sterling, G. Theron, A. Weinberg, A. Gupta and P. Denti, Pharmacokinetics and Drug-Drug Interactions of Isoniazid and Efavirenz in Pregnant Women Living With HIV in High TB Incidence Settings: Importance of Genotyping, *Clin. Pharmacol. Ther.*, **109**, 1034 (2021); https://doi.org/10.1002/cpt.2044
62. C.M. Lee, S.S. Lee, J.M. Lee, H.C. Cho, W.S. Kim, H.J. Kim, C.Y. Ha, H.J. Kim, T.H. Kim, W.T. Jung and O.J. Lee, Early Monitoring for Detection of Antituberculous Drug-induced Hepatotoxicity, *Korean J. Intern. Med.*, **31**, 65 (2016); https://doi.org/10.3904/kjim.2016.31.1.65
63. B. Myers, T.C. Bouton, E.J. Ragan, L.F. White, H. McIlleron, D. Theron, C.D.H. Parry, C.R. Horsburgh, R.M. Warren and K.R. Jacobson, Impact of Alcohol Consumption on Tuberculosis Treatment Outcomes: A Prospective Longitudinal Cohort Study Protocol, *BMC Infect. Dis.*, **18**, 488 (2018); https://doi.org/10.1186/s12879-018-3396-y
64. J.T. Wilcke, M. Døssing, H.R. Angelo, D. Askgaard, A. Rønn and H.R. Christensen, Unchanged Acetylation of Isoniazid by Alcohol Intake, *Int. J. Tuberc. Lung Dis.*, **8**, 1373 (2004).
65. S.A. Gilroy, M.A. Rogers and D.C. Blair, Treatment of Latent Tuberculosis Infection in Patients Aged ≥35 Years, *Clin. Infect. Dis.*, **31**, 826 (2000); https://doi.org/10.1086/314037
66. M. Stettner, D. Steinberger, C.J. Hartmann, T. Pabst, L. Konta, H.P. Hartung and B.C. Kieseier, Isoniazid-Induced Polyneuropathy in a Tuberculosis Patient – Implication for Individual Risk Stratification with Genotyping?, *Brain Behav.*, **5**, e00326 (2015); https://doi.org/10.1002/brb3.326
67. A.T. Mafukidze, M. Calnan and J. Furin, Peripheral Neuropathy in Persons with Tuberculosis, *J. Clin. Tuberc. Other Mycobact. Dis.*, **2**, 5 (2016); https://doi.org/10.1016/j.jctube.2015.11.002
68. M. Si, H. Li, Y. Chen and H. Peng H. Ethambutol and Isoniazid Induced Severe Neurotoxicity in a Patient Undergoing Continuous Ambulatory Peritoneal Dialysis, *Case Rep.*, **2018**, bcr2017223187 (2018); https://doi.org/10.1136/bcr-2017-223187
69. D.E. Snider Jr., Pyridoxine Supplementation During Isoniazid Therapy, *Tubercle*, **61**, 191 (1980); https://doi.org/10.1016/0041-3879(80)90038-0
70. M. Bhargava and A. Bhargava, Pyridoxine for Patients Suffering from Drug-Susceptible Tuberculosis in India, *Public Health Action*, **8**, 97 (2018); https://doi.org/10.5588/pha.18.0017
71. P.S. Patil, S.L. Kasare, N.B. Haval, V.M. Khedkar, P.P. Dixit, E.M. Rekha, D. Sriram and K.P. Haval, Novel Isoniazid Embedded Triazole Derivatives: Synthesis, Antitubercular and Antimicrobial Activity Evaluation, *Bioorg. Med. Chem. Lett.*, **30**, 127434 (2020); https://doi.org/10.1016/j.bmcl.2020.127434
72. A.L. Goldman and S.S. Braman, Isoniazid: A Review with Emphasis on Adverse Effects, *Chest*, **62**, 71 (1972); https://doi.org/10.1378/chest.62.1.71
73. A.K. Dutt, D. Moers and W.W. Stead, Undesirable Side Effects of Isoniazid and Rifampin in Largely Twice-Weekly Short-Course Chemotherapy for Tuberculosis, *Am. Rev. Respir. Dis.*, **128**, 419 (1983); https://doi.org/10.1164/arrd.1983.128.3.419
74. B.B. Maiha, A. Bako, S. Anafi, M.S. Yusuf and A.M. Kabiru, Amelioration of Isoniazid induced Oxidative Stress and Hematotoxicity by Vitamin C in Wistar Rats, *Nigerian J. Pharm. Appl. Sci. Res.*, **9**, 23 (2020).
75. N.A. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennernas, A.S. Hussain, H.E. Junginger, S.A. Stavchansky, K.K. Midha, V.P. Shah and G.L. Amidon, Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification, *Mol. Pharm.*, **1**, 85 (2004); https://doi.org/10.1021/mp034006h

76. T.T. Mariappan and S. Singh, Regional Gastrointestinal Permeability of Rifampicin and Isoniazid (Alone and their Combination) in the Rat, *Int. J. Tuberc. Lung Dis.*, **7**, 797 (2003).
77. C. Becker, J.B. Dressman, G.L. Amidon, H.E. Junginger, S. Kopp, K.K. Midha, V.P. Shah, S. Stavchansky and D.M. Barends, Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Isoniazid, *J. Pharm. Sci.*, **96**, 522 (2007); https://doi.org/10.1002/jps.20765
78. K.V. Rao, S. Kailasam, N.K. Menon and S. Radhakrishna, Inactivation of Isoniazid by Condensation in a Syrup Preparation, *Bull. World Health Organ.*, **45**, 625 (1971).
79. M.Y. Lin, S.J. Lin, L.C. Chan and Y.C. Lu, Impact of Food and Antacids on the Pharmacokinetics of Anti-tuberculosis Drugs: Systematic Review and Meta-Analysis, *Int. J. Tuberc. Lung Dis.*, **14**, 806 (2010).
80. M.R. Holdiness, Clinical Pharmacokinetics of the Antituberculosis Drugs, *Clin. Pharmacokinet.*, **9**, 511 (1984); https://doi.org/10.2165/00003088-198409060-00003
81. A. Tostmann, M.J. Boeree, R.E. Aarnoutse, W.C. De Lange, A.J. Van Der Ven and R. Dekhuijzen, Antituberculosis Drug-Induced Hepatotoxicity: Concise Up-to-date Review, *J. Gastroenterol. Hepatol.*, **23**, 192 (2008); https://doi.org/10.1111/j.1440-1746.2007.05207.x
82. P. Preziosi, Isoniazid: Metabolic Aspects and Toxicological Correlates, *Curr. Drug Metab.*, **8**, 839 (2007); https://doi.org/10.2174/138920007782798216
83. S. Mahapatra, L.K. Woolhiser, A.J. Lenaerts, J.L. Johnson, K.D. Eisenach, M.L. Joloba, W.H. Boom and J.T. Belisle, A Novel Metabolite of Antituberculosis Therapy Demonstrates Host Activation of Isoniazid and Formation of the Isoniazid-NAD^+ Adduct, *Antimicrob. Agents Chemother.*, **56**, 28 (2012); https://doi.org/10.1128/AAC.05486-11
84. K. Fukino, Y. Sasaki, S. Hirai, T. Nakamura, M. Hashimoto, F. Yamagishi and K. Ueno, Effects of N-Acetyltransferase 2 (NAT2), CYP2E1 and Glutathione-S-transferase (GST) Genotypes on the Serum Concentrations of Isoniazid and Metabolites in Tuberculosis Patients, *J. Toxicol. Sci.*, **33**, 187 (2008); https://doi.org/10.2131/jts.33.187
85. K.F. Windmill, A. Gaedigk, P. de la M. Hall, H. Samaratunga, D.M. Grant and M.E. McManus, Localization of N-Acetyltransferases NAT1 and NAT2 in Human Tissues, *Toxicol. Sci.*, **54**, 19 (2000); https://doi.org/10.1093/toxsci/54.1.19
86. I.G. Metushi, P. Cai, X. Zhu, T. Nakagawa and J.P. Uetrecht, A Fresh Look at the Mechanism of Isoniazid-Induced Hepatotoxicity, *Clin. Pharmacol. Ther.*, **89**, 911 (2011); https://doi.org/10.1038/clpt.2010.355
87. L. Scharer and J.P. Smith, Serum Transaminase Elevations and Other Hepatic Abnormalities in Patients Receiving Isoniazid, *Ann. Intern. Med.*, **71**, 1113 (1969); https://doi.org/10.7326/0003-4819-71-6-1113
88. Y.S. Huang, Recent Progress in Genetic Variation and Risk of Antituberculosis Drug-Induced Liver Injury, *J. Chin. Med. Assoc.*, **77**, 169 (2014); https://doi.org/10.1016/j.jcma.2014.01.010
89. R.A. Garibaldi, R.E. Drusin, S.H. Ferebee and M.B. Gregg, Isoniazid-Associated Hepatitis Report of an Outbreak, *Am. Rev. Respir. Dis.*, **106**, 357 (1972); https://doi.org/10.1164/arrd.1972.106.3.357
90. S. Tafazoli, M. Mashregi and P.J. O'Brien, Role of Hydrazine in Isoniazid-induced Hepatotoxicity in a Hepatocyte Inflammation Model, *Toxicol. Appl. Pharmacol.*, **229**, 94 (2008); https://doi.org/10.1016/j.taap.2008.01.002
91. G. Ramachandran and S. Swaminathan, Role of Pharmacogenomics in the Treatment of Tuberculosis: A Review, *Pharmgenomics Pers. Med.*, **5**, 89 (2012); https://doi.org/10.2147/PGPM.S15454
92. C.M. Nolan, S.V. Goldberg and S.E. Buskin, Hepatotoxicity Associated With Isoniazid Preventive Therapy, A 7-Year Survey from a Public Health Tuberculosis Clinic, *JAMA*, **281**, 1014 (1999); https://doi.org/10.1001/jama.281.11.1014
93. P.R. Donald, Antituberculosis Drug-Induced Hepatotoxicity in Children, *Pediatr. Rep.*, **3**, e16 (2011); https://doi.org/10.4081/pr.2011.e16
94. D.A. Perwitasari, J. Atthobari and B. Wilffert, Pharmacogenetics of Isoniazid-Induced Hepatotoxicity, *Drug Metab. Rev.*, **47**, 222 (2015); https://doi.org/10.3109/03602532.2014.984070
95. A.N. Unissa, S. Subbian, L.E. Hanna and N. Selvakumar, Overview on Mechanisms of Isoniazid Action and Resistance in *Mycobacterium tuberculosis*, *Genetics and evolution*, **45**, 474 (2016); https://doi.org/10.1016/j.meegid.2016.09.004
96. A. Cattamanchi, R.B. Dantes, J.Z. Metcalfe, L.G. Jarlsberg, J. Grinsdale, L.M. Kawamura, D. Osmond, P.C. Hopewell and P. Nahid, Clinical Characteristics and Treatment Outcomes of Patients with Isoniazid-Monoresistant Tuberculosis, *Clin. Infect. Dis.*, **48**, 179 (2009); https://doi.org/10.1086/595689
97. D. Menzies, A. Benedetti, A. Paydar, S. Royce, M. Pai, W. Burman, A. Vernon and C. Lienhardt, Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-Resistance to Isoniazid: A Systematic Review and Meta-Analysis, *PLoS Med.*, **6**, e1000150 (2009); https://doi.org/10.1371/journal.pmed.1000150
98. H.E. Jenkins, M. Zignol and T. Cohen, Quantifying the Burden and Trends of Isoniazid Resistant Tuberculosis, 1994–2009, *PLoS One*, **6**, e22927 (2011); https://doi.org/10.1371/journal.pone.0022927
99. G. Singh, H. Dwivedi, S.K. Saraf and S.A. Saraf, Niosomal Delivery of Isoniazid - Development and Characterization, *Trop. J. Pharm. Res.*, **10**, 203 (2011); https://doi.org/10.4314/tjpr.v10i2.66564
100. C. Vilchèze and W.R. Jacobs Jr., Resistance to Isoniazid and Ethionamide in *Mycobacterium tuberculosis*: Genes, Mutations and Causalities, *Microbiol. Spectr.*, MGM2-0014-2013 (2014); https://doi.org/10.1128/microbiolspec.MGM2-0014-2013
101. D.A. Rouse and S.L. Morris, Molecular Mechanisms of Isoniazid Resistance in *Mycobacterium tuberculosis* and *Mycobacterium bovis*, *Infect. Immun.*, **63**, 1427 (1995); https://doi.org/10.1128/iai.63.4.1427-1433.1995
102. S. Siddiqi, P. Takhar, C. Baldeviano, W. Glover and Y. Zhang, Isoniazid Induces Its Own Resistance in Nonreplicating *Mycobacterium tuberculosis*, *Antimicrob. Agents Chemother.*, **51**, 2100 (2007); https://doi.org/10.1128/AAC.00086-07
103. R.S. Wallis, M. Palaci and K. Eisenach, Persistence, Not Resistance, Is the Cause of Loss of Isoniazid Effect, *J. Infect. Dis.*, **195**, 1870 (2007); https://doi.org/10.1086/518044
104. H.M. Blumberg, W.J. Burman, R.E. Chaisson and C.L. Daley, Treatment of Tuberculosis, *Am. J. Respir. Crit. Care Med.*, **167**, 603 (2003); https://doi.org/10.1164/rccm.167.4.603