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REVIEW

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Nyctanthes arbor-tristis L.: Perspective of phytochemical-based inhibition of fatty acid biosynthesis in *Mycobacterium tuberculosis*

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ABSTRACT

Nyctanthes arbor-tristis L. contains various phytochemicals with tremendous potential to fight against different infections. However, the effect of these phytochemicals on *Mycobacterium tuberculosis* is yet unknown. Treatment of multi-drug resistance (MDR) and extensively drug-resistant (XDR) strains of the tuberculosis bacterium are still challenging. Therefore, there is an urgent need to overcome this problem. The present review focuses on the potential action of the hypolipidemic phytochemicals obtained from *N. arbor-tristis* on the growth and survival of *M. tuberculosis* in the human host. The extracts from different parts of this plant are hypolipidemic by various established mechanisms. Phytochemicals like iridoids and flavonoids from plant origin exhibit a high capacity to regulate cholesterol and fatty acid biosynthesis *in vivo*. The hypolipidemic properties of *N. arbor-tristis*-derived extracts are probably due to the presence of phytochemicals such as iridoids, flavonoids, etc. It may regulate fatty acid biosynthesis in *M. tuberculosis* by targeting bacterial fatty acid synthase enzyme. Additionally, these phytochemicals also inhibit cholesterol biosynthesis in the host by interrupting the function of HMG-CoA reductase. *M. tuberculosis* is an intracellular pathogen. It is also established fact as on date that entry of tuberculosis bacterium in the macrophage is macrophage membrane cholesterol-dependent. Host cholesterol is also otherwise necessary by multiple mechanisms for the pathogenesis of tuberculosis. Based on the above facts, we believe that *N. arbor-tristis* derived phytochemicals can act both on the tuberculosis bacterium and on the host for prevention and cure of tuberculosis.

1. Introduction

The management of tuberculosis has become far more complex due to the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. In 2020, estimated new tuberculosis cases were around 10 million, while 1.5 million people are died due to the pathogen (WHO, 2021). The current treatment strategy against *M. tuberculosis* includes isoniazid, rifampin, ethambutol, pyrazinamide. It is shown that multidrug-resistant tuberculosis (MDR-TB) is developed due to the resistance of commonly used antimycobacterial agents (Chang et al., 2020; Kim et al., 2019; Sullivan and Amor, 2016). Even extensively drug-resistant (XDR-TB) strains of *M. tuberculosis* are becoming a global problem (Manjelievskaia et al., 2016). Therefore, there is an urgent need to evaluate new or alternative therapeutics to manage tuberculosis patients.

Medicinal plants and herbal products are used to prepare several life-saving medicines. In traditional systems of medicine, various plants are still in use for therapeutic purposes. In the Unani System of medicine, *Nyctanthes arbor-tristis* L. is used as therapeutic (Ahmed et al., 2015). Extracts prepared from different medicinal plants have shown antimycobacterial effects (Gupta et al., 2010). *N. arbor-tristis* extracts have shown antibiotic properties against several microorganisms (Khatune et al., 2001).

The flower extracts obtained from *N. arbor-tristis* exhibits hypolipidemic activity *in vivo* (Rangika et al., 2015). Some phytochemicals present in the plant must be responsible for such hypolipidemic property in the host. Phytochemicals like iridoid glycosides and flavonoids are found extensively in different plant parts of *N. arbor-tristis* (Rathore et al., 1990). Iridoids are secondary metabolites synthesized by various plants, which can be found as

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intermediates in alkaloids synthesis (Dinda et al., 2007). Iridoids like plumericin and isoplumericin, isolated from *Plumeria* (a flowering tree), have a tremendous role in inhibiting mycobacterial growth (Kumar et al., 2013). Extracts from various parts of *N. arbor-tristis* like seeds, leaves, flowers, bark, and fruits consist of different phytochemicals, namely flavonol glycoside, oleanolic acid, essential oils, tannic acid, carotene, friedeline, lupeol, glucose, and benzoic acid (Sah and Verma, 2012). *N. arbor-tristis* extracts have already been recognized as hepatoprotective agents. It has antileishmanial, antiviral, antifungal, antipyretic, antihistaminic, antimalarial, antibacterial, anti-inflammatory, and antioxidant properties as well (Sah and Verma, 2012; Chaudhary et al., 2018). Moreover, major iridoid glycosides like arbortristoside A, B, C, and 6β-hydroxyloganin have also been found in *N. arbor-tristis,* and these iridoids are shown to be effective as antiviral and antileishmanial agents (Gupta et al., 2005; Tandon et al., 1991).

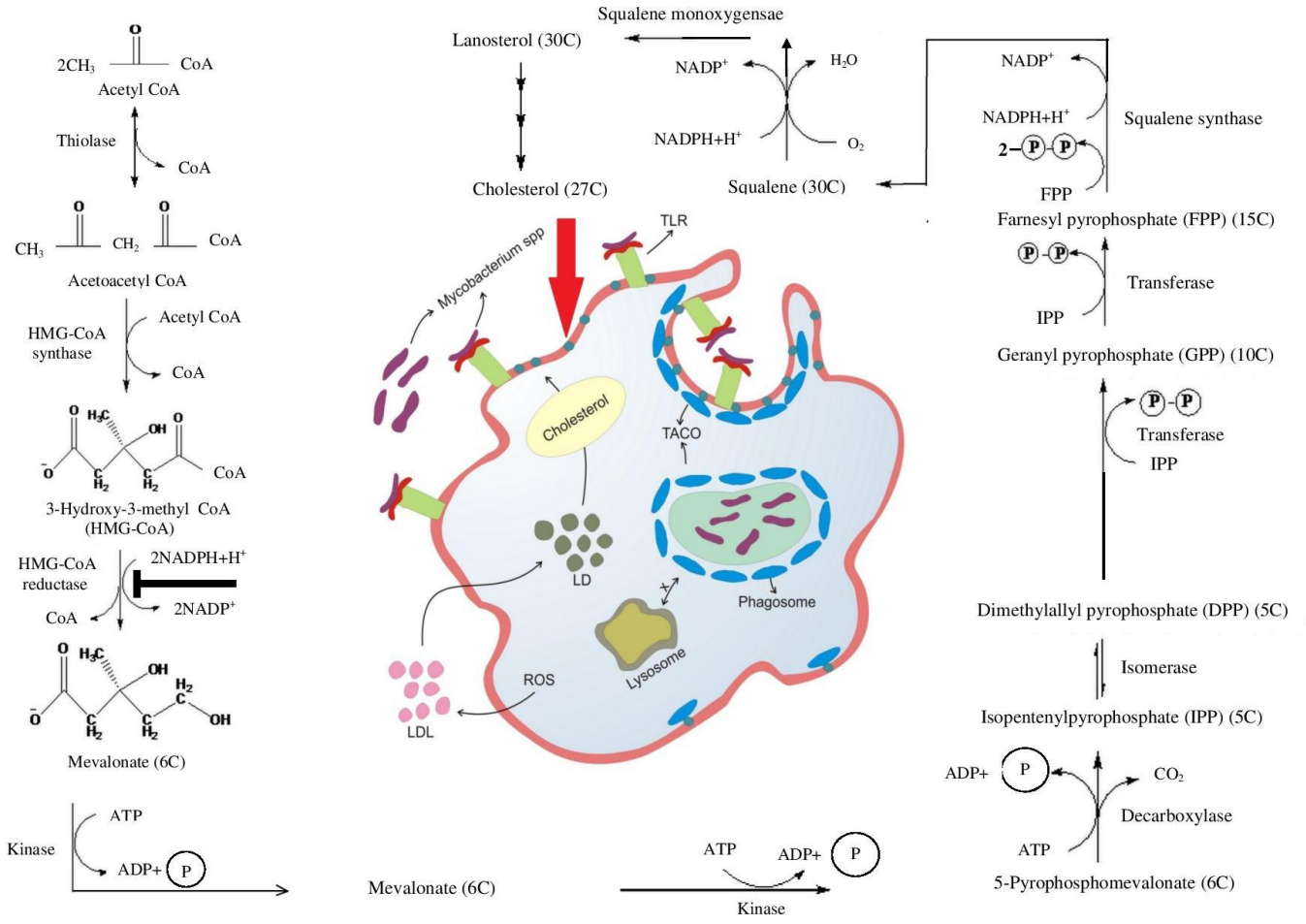

Figure 1. Schematic diagram showing the important enzymatic reactions involved in the intracellular persistence and pathogenesis of *M. tuberculosis* inside host macrophage

The synthesis of cholesterol facilitates the entry and uptake of *M. tuberculosis* inside the macrophage. Reactive oxygen species (ROS) may oxidize low-density lipoproteins (LDL), which subsequently results in the formation of lipid droplets (LD) inside the macrophage. Additionally, cholesterol helps to arrange TACO proteins around the phagosome and prevents phagolysosome complex formation. This mechanism subsequently facilitates the survival and persistence of *M. tuberculosis* inside the macrophage.*N. arbor-tristis* phytochemicals may inhibit the function of HMG-CoA reductase, which ultimately interrupts the bacterial survival and persistence. "⊥" sign represents the inhibitory action of *N. arbor-tristis* phytochemicals.

Iridoids are proved to inhibit fatty acid biosynthesis. Iridoid-glycoside (e.g., ipolamiide) can inhibit type II fatty acid synthase acting through FabI (enoyl acyl carrier protein ACP reductase or enoyl ACP reductase) in *Plasmodium falciparum* (Kirmizibekmez et al., 2004). *M. tuberculosis* uses fatty acid synthase, an essential enzyme for fatty acid biosynthesis and a sole carbon source (Muñoz-Elías and McKinney, 2005). Fatty acid biosynthesis leads to produce propenyl CoA and mycolic acid, which in turn help to compose the cell wall of *M. tuberculosis* (Lee et al., 2013; Korf et al., 2005). Therefore, we feel that iridoids like arbortristoside A, B, C, and 6β-hydroxyloganin (or some other iridoids) present in *N. arbor-tristis* may also reduce the growth of *M. tuberculosis* by interrupting fatty acid synthase activity acting through FabI inhibition. In this context, we wish to emphasize that host fatty acids can also modulate the pathogenesis of tuberculosis (Russell, 2003). So, if iridoids inhibit host fatty acid biosynthesis, that will be an attractive mechanism for controlling tuberculosis. However, as of date, there is evidence that *N. arbor-tristis*-derived products reduce triglyceride in the host (Rathod et al., 2009; Rangika et al., 2015). This reduction of triglycerides is due to the control of insulin sensitivity or direct inhibition of fatty acid biosynthesis in the host is not very clear as on date. Keeping this controversy alive, it can be logically concluded that the plant products can control tuberculosis because diabetes mellitus is also a risk factor for tuberculosis (Dooley and Chaisson, 2009). So, control of diabetes mellitus by the products of *N. arbor-tristis* as reported in various literature, may improve the tuberculosis status at least in a diabetic host (Rangika et al., 2015; Kul et al., 2015).

Additionally, cholesterol biosynthesis plays a significant role in the intracellular persistence of *M. tuberculosis* (Miner et al., 2009).

Therefore, inhibiting cholesterol synthesis might be an alternative strategy to inhibit *M. tuberculosis*. Several plant-derived phytochemicals have been shown to inhibit cholesterol synthesis by inhibiting HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) or degrading lipid moieties (Middleton and Kok-Pheng, 1982; Reddy Palvai and Urooj, 2014; Palu et al., 2012). Hence, it is logical to think that iridoid glycosides, extracted from *N. arbor-tristis*, may decrease the survival of *M. tuberculosis* by reducing cholesterol biosynthesis through inhibition of HMG-CoA reductase. Apart from iridoids, several flavonoids like nicotiflorin, phenylpropanoid, naringenin-4'-*O*-β-D-glucopyranosyl-α-xylopyranoside, astragalin, etc. are found in *N. arbor-tristis*. Flavonoids from leaf extract of various plants are shown to exert a high degree of fatty acid synthase inhibition (Chen et al., 2009). On the other hand, flavonoids can lower cholesterol levels by inhibiting the function of HMG-CoA reductase (Baskaran et al., 2015). Hence, we believe that flavonoids present in *N. arbor-tristis* may reduce the growth and survival of *M. tuberculosis* by inhibiting HMG-CoA reductase. Critical ethnopharmacological review is already available for the plant concerned (Agrawal and Pal, 2013). However, from a mechanistic point of view, we feel that phytochemicals obtained from *N. arbor-tristis* have significant potential for preventing and curing tuberculosis, and this aspect is reviewed here. We consider that such a review of basic biology and ethnopharmacological relevance related to the context is necessary for novel drug discovery to prevent and cure tuberculosis.

2. Methodology

A thorough literature survey has been done to review the studies published so far in the concerned field available freely on public domains such as Pubmed and Google Scholar. Original studies, review articles, and books are referred to as search articles related to the present review article from 1977 to 2021. "*Nyctanthes arbor-tristis* L." as a keyword is predominantly used to cite reference articles. However, other keywords such as "*Mycobacterium tuberculosis*", iridoid, cholesterol, fatty acid, HMG-CoA reductase are also associated with *N. arbor-tristis*. Only peer-reviewed publications related to the keywords mentioned above have been included in this article. In contrast, articles published in other languages except English are excluded.

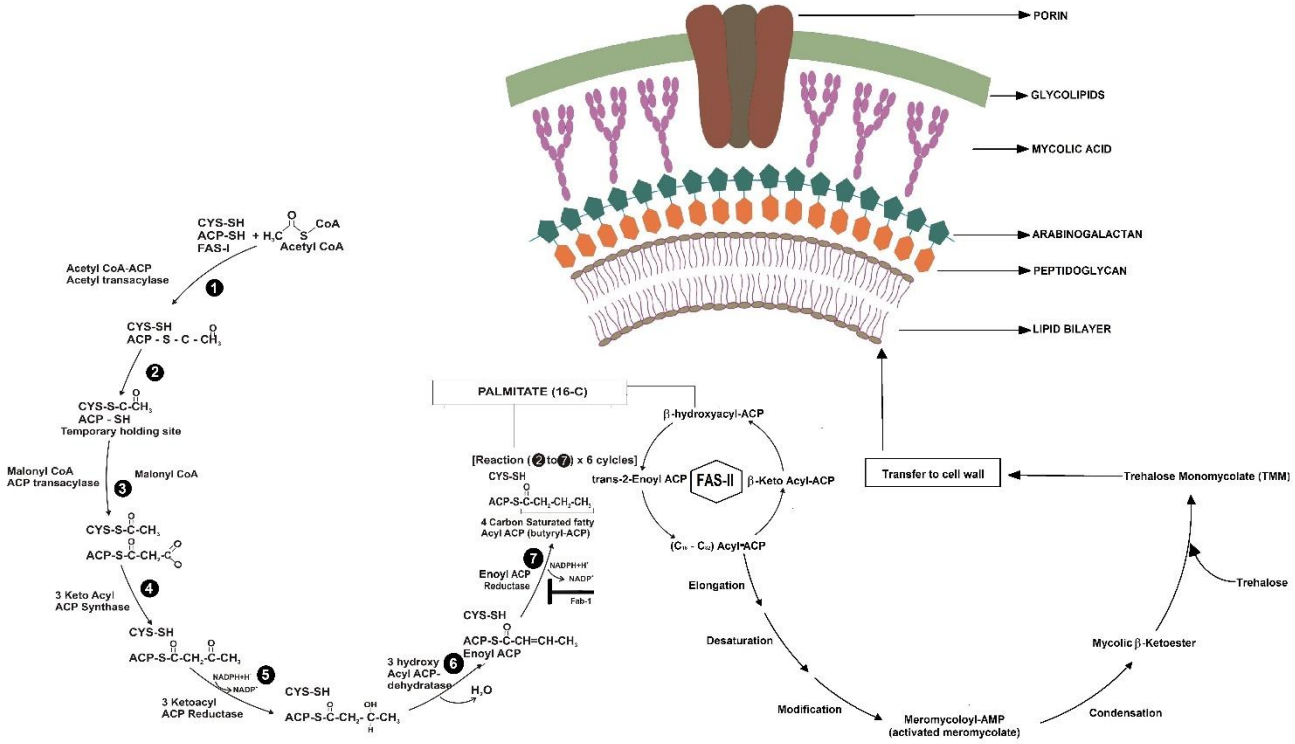

Figure 2. Schematic diagram representing the probable enzymatic reactions mediated combinedly by FAS-I and FAS-II by *M. tuberculosis* to synthesize long-chain fatty acyl ester

N. arbor-tristis phytochemicals may inhibit the function of Enoyl ACP reductase, which ultimately results in the inhibition of *M. tuberculosis* cell wall synthesis. "⊥" sign represents the inhibitory action of *N. arbor-tristis* phytochemicals.

3. The role of cholesterol in the pathogenesis of *M. tuberculosis*

Cholesterol is an essential constituent of the plasma membrane, which provides fluidity and permeability (Ikonen, 2008). Additionally, cholesterol acts as a vital precursor for synthesizing bile salts, steroid hormones, and vitamin D. Animals readily synthesize cholesterol. Even fungi and plants are also capable of producing cholesterol. However, sterol biosynthesis is still contentious in bacteria (Fuerst and Sagulenko, 2014). *M. tuberculosis* lacks cholesterol biosynthesis machinery like monooxygenase etc. (Podust et al., 2004). Therefore, the "smart bacteria" *M. tuberculosis* uses the host cholesterol to maintain its pathogenesis and intracellular persistence (Figure 1). Interestingly, host cholesterol plays as a triggering factor in tuberculosis development (Miner et al., 2009). Even extra consumption of dietary cholesterol may influence the virulence mechanism of *M. tuberculosis* (Schafer et al., 2009). Besides, cholesterol is required to anchor host protein coronin 1 or tryptophan-aspartate-containing coat protein (TACO) on the surface of the phagosome. TACO inhibits the phagosome-lysosome fusion during infection (Anand and Kaul,

2005). Hence, inhibiting cholesterol biosynthesis may be a step forward to control mycobacterial survival. It is particularly relevant in the present context since *M. tuberculosis* enters the host macrophage through the cholesterol-rich region of the macrophage membrane (Gatfield and Pieters, 2000).

4. Fatty acid synthase and mycobacterial growth

Fatty acid synthase (E.C. 2.3.1.85) is an essential enzyme for *M. tuberculosis* to synthesize long-chain fatty acid through sequential condensation of acetyl-coenzyme A (acetyl-CoA) and malonyl-CoA (Ngo et al., 2007). This enzyme needs to produce the major cell wall components like mycolic acid etc. (Figure 2). Fatty acid biosynthesis is crucial for *M. tuberculosis* for its intracellular persistence because, in the presence of host-derived fatty acid, this bacteria is survived by isocitrate lyase of glyoxylate cycle (Gould et al., 2006). The complex cell wall structure contributes to less permeability and fluidity. This helps *M. tuberculosis* to develop resistance towards multiple drugs when surviving in a protected phagosome that does not fuse with the lysosome (Ciccarelli et al., 2013). Therefore, new drugs may be designed to target bacterial cell wall synthesis. Mycobacterial fatty acid biosynthesis mainly depends on type I (FAS I) and type II (FAS II) fatty acid synthase. FAS I is present in mammalian and higher eukaryotes, whereas FAS II is present only in prokaryotes. The complete enzymatic process of mycobacterial fatty acid biosynthesis is poorly understood as of date due to the slow growth of the bacterium in the available culture systems. However, it is known beyond any doubt that both FAS I and FAS II systems are essential for the synthesis of C80 mycolic acid. Initially, FAS I synthesizes C16-C26 acyl-CoA esters, ultimately producing C80 mycolic acid by FAS II (Cole et al., 1998).

5. Inhibition of long-chain fatty acid biosynthesis as a measure for controlling tuberculosis

As mentioned earlier, fatty acid biosynthesis is necessary to synthesize major cell wall components, thus crucial for bacterial survival and drug resistance. Several studies have shown the inhibition of this bacterium by either targeting fatty acid synthase or mycolic acid formation. Ngo et al. (2007) have shown that pyrazinamide (PZA) and its analog of 5-chloropyrazinamide (5-Cl-PZA) can inhibit FAS I in *M. smegmatis*. Moreover, 2-hexadecynoic acid and 2-octadecynoic acid show bactericidal effects against *M. smegmatis* and *M. bovis*. Having higher concentrations, 2-octadecynoic acid accumulates 3-ketohexadecanoic acid, which further inhibits fatty acid biosynthesis and formation of mycolic acid (Morbidoni et al., 2006). Isoxyl and thiacetazone cause the accumulation of 3-hydroxy C18, C20, and C22 fatty acids, which ultimately inhibit the dehydratase step of the fatty acid synthase type II-mediated elongation (Grzegorzewicz et al., 2012a). Besides, adamantyl urea-based compound is also being employed successfully to inhibit mycolic acid transport across the plasma membrane (Grzegorzewicz et al., 2012b).

6. Recent approaches to inhibit cholesterol biosynthesis in tuberculosis

The persistence of *M. tuberculosis* mainly depends on utilizing the host cholesterol (Pandey and Sassetti, 2008). Apart from this, the cellular lipids play a pivotal role in the progression towards the latent stage (Ahmad et al., 2006; Ouellet et al., 2011). So, the inhibition of cholesterol synthesis may affect the survival of the bacteria. Recent strategies comprise a classical mechanism to inhibit cholesterol synthesis, which is based on the inhibition of HMG-CoA reductase (Parihar et al., 2014). HMG-CoA reductase is an essential enzyme that catalyzes HMG-CoA conversion to mevalonate in cholesterol biosynthesis (Endo, 2010) (Figure 1). In the year 1977, it has been first reported that citrinin can reduce cholesterol levels by inhibiting HMG-CoA reductase (Kazuhiko et al., 1977). In broadway, cholesterol-lowering drugs can be classified into two major groups-statins (e.g., lovastatin, atorvastatin, etc.) and fibrates (e.g., ciprofibrate, bezafibrate, etc.) (Pahan, 2006). The mechanism of statin is based on the competitive inhibition of HMG-CoA reductase, whereas fibrates stimulate β-oxidation of fatty acids in peroxisomes and mitochondria. Moreover, statins are hypothesized to treat *M. tuberculosis* as it potentially inhibits HMG-CoA reductase (Parihar et al., 2014). However, these drugs are still not safe due to their toxic side effects (Endo, 2010; Golomb and Evans, 2008). Therefore, alternative approaches are required, which would have less toxicity.

7. Medicinal plant extracts against *M. tuberculosis*

Medicinal plants have a significant role in controlling the growth of *M. tuberculosis*. Extracts from different parts of plants are used to treat *M. tuberculosis,* and among them, the leaf extract is supposed to be more active (Gupta et al., 2010). Leaf extract from *Allium cepa* L., *A. sativum* L., and *Aloe vera* L. Burm. F. have shown antitubercular activity up to 68% against H37Rv strain (Gupta et al., 2010). Extracts prepared from various plants are proved to be bactericidal for several mycobacterial species, including MDR strains of *M. tuberculosis* (Bueno-Sánchez et al., 2009; Lawal et al., 2014; Mariita et al., 2010; Sheeba et al., 2015; Shukla and Sharma, 2021; Sivakumar and Jayaraman, 2011).

8. Inhibition of cholesterol biosynthesis by different herbal extracts and phytochemicals

As mentioned earlier, cholesterol biosynthesis plays a crucial role in the intracellular survival of *M. tuberculosis*. In this stage, the bacterium uses the host cholesterol from the plasma membrane and accumulates the lipid droplets into the macrophage (Daniel et al., 2011). It is now proved that many medicinal plants contain phytochemicals that inhibit cholesterol biosynthesis. The leaf extract of *Basella alba* L. has phytochemicals such as α-tocopherol, oleic acid, apigenin, luteolin, ascorbic acid, naringin, and eicosyl ester are reported to inhibit HMG-CoA reductase *in vivo* (Baskaran et al., 2015). Additionally, iridoids and precursors like picroliv, oleuropein, geraniol, and limonene can act as hypolipidemic agents (Khanna et al., 1994; Omar, 2010; Pattanayak et al., 2009). While, monoterpene like rowachol successfully inhibits HMG-CoA reductase in the rat model (Middleton and Kok-Pheng, 1982). *Morinda citrifolia* L. extracts alone or in combination with iridoid are shown to inhibit HMG-CoA reductase (Palu et al., 2012; West et al., 2014).

On the other hand, flavonoids are the secondary metabolites of plants, which are synthesized through the phenylpropanoid pathway (Falcone Ferreyra et al., 2012). Flavonoids from plant origin have shown tremendous cholesterol-lowering effects *in vivo* (Esmaillzadeh et al., 2006; Miyake et al., 2006; Roza et al., 2007). Flavonoids obtained from *B. alba* leaf extract exert the inhibition of HMG-CoA reductase activity (Baskaran et al., 2015).

9. Antimycobacterial effects of *N. arbor-tristis*

So far, we have illustrated the importance of different medicinal plants and phytochemicals having antimycobacterial activity, cholesterol-lowering ability, and inhibitory role in fatty acid biosynthesis. There is evidence regarding the medicinal effect of extracts from different parts of *N. arbor-tristis* in various infectious diseases (Rahman et al., 2013; Murti et al., 2012) as well as in

metabolic disorders (Agrawal and Pal, 2013; Khatune et al., 2001) (Figure 3). Additionally, the flower extract exhibits hypolipidemic activity in the mice model (Rangika et al., 2015). The antimycobacterial effect and hypolipidemic characteristics of the plant extract may be due to the presence of different phytochemicals. The two most important classes of phytochemicals found in *N. arbor-tristis* are iridoid glycosides (e.g., arbortristoside-A, B, C, 6β-hydroxyloganin, etc.) and flavonoids (e.g., nicotiflorin, phenylpropanoid, naringenin-4'-*O*-β-D-glucopyranosyl-α-xylopyranoside, astragalin, etc.) (Table 1). Unlike the other iridoids, monoterpenes such as loganins are produced from the non-mevalonate pathway (Eichinger et al., 1999). Loganin glycoside extracted from plant sources can act as a hypolipidemic substance by regulating PI3K–Akt/PKB signaling pathway (Yamabe et al., 2010; Kang et al., 2018). In context, 6β-hydroxyloganin obtained from *N. arbor-tristis* is reported as anti-leishmania and anti-arthritic agents (Tandon et al., 1991).

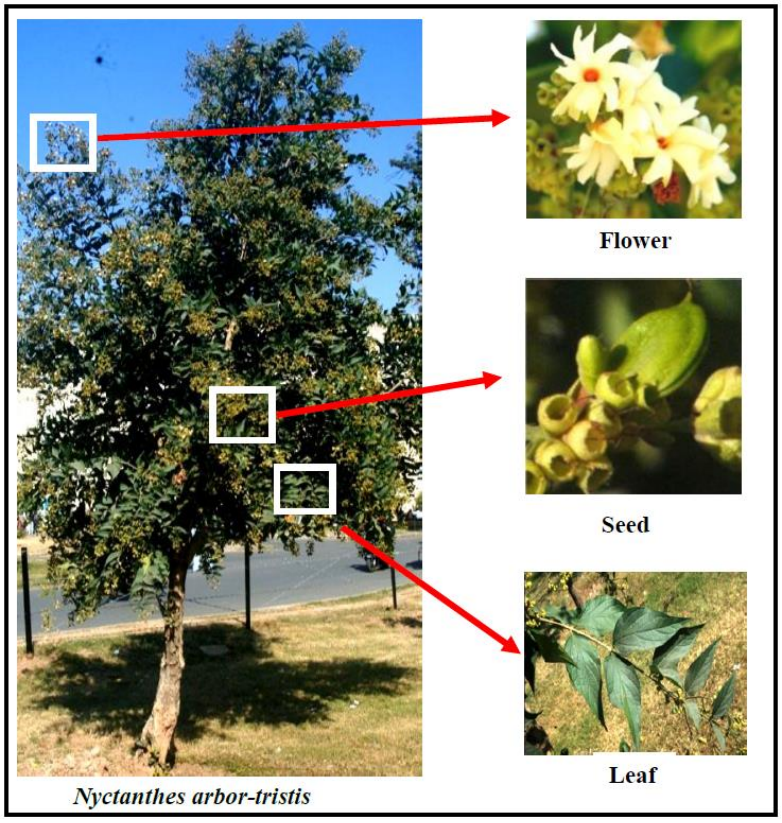

Figure 3. Photograph showing *N. arbor-tristis* tree and its different parts such as flower, seed, and leaf

For a long time, medicinal plants have been used in the Indian traditional "Ayurveda" to treat different infectious diseases, including pulmonary tuberculosis (Debnath et al., 2012). As mentioned earlier, different herbs exhibited antitubercular effects against specific mycobacterial species, including drug-resistant strains. Besides, plant phytochemicals like iridoid glycosides, flavonoids, terpenoids are capable of inhibiting the growth of *M. tuberculosis* by an unknown mechanism and are reported as a novel antituberculosis drug (Askun et al., 2013; Cantrell et al., 2001; Gordien et al., 2009; Jimenez-Arellanes et al., 2013; Kumar et al., 2013; Zheng et al., 2014). These phytochemicals have different intracellular targets with potential for cholesterol biosynthesis inhibition, fatty acid synthase inhibition, etc. (Duan et al., 2012; Khanna et al., 1994; Kirmizibekmez et al., 2004; Li et al., 2014; Sundaram et al., 2013; Tasdemir et al., 2005; Wang et al., 2012; Yamabe et al., 2007).

Iridoids obtained from plant sources show the potential therapeutic role against trypanosomiasis and leishmaniasis parasites. Iridoid-rich plant extracts can cease fatty acid biosynthesis in *Plasmodium falciparum* by inhibiting FabI enzyme activity (Tasdemir et al., 2005). *M. tuberculosis* is an intracellular pathogen like *P. falciparum*, *Trypanosoma bruceirhodesiense*, *Leishmania donovani*; therefore, we believe that the iridoid glycosides like arbortristosides A, B, C, etc. obtained from the extract of *N. arbor-tristis* may also exert the inhibitory role against *M. tuberculosis* by analogous mechanism.

10. Hypothetical interventions

M. tuberculosis has a tremendous capacity to use the host machinery for their survival and intracellular persistence. One of the important mechanisms of *M. tuberculosis* pathogenesis is based on the utilization of host cholesterol (Ahmad et al., 2006; Ouellet et al., 2011; Pandey and Sassetti, 2008). Further, fatty acid biosynthesis is crucial for the bacterium to produce cell wall components like mycolic acid (Takayama et al., 2005). The importance of cholesterol biosynthesis inhibition is believed to be an important method for preventing and curing tuberculosis (Parihar et al., 2014). Cholesterol biosynthesis inhibition also increases the bacteriocidal effects of known antimycobacterial drugs (Lobato et al., 2014). Inhibition of bacterium fatty acid biosynthesis, particularly mycolic acid biosynthesis, is caused by established antimycobacterial drugs (Schroeder et al., 2002).

Considering the above facts, we believe that extracts of *N. arbor-tristis* may cause cholesterol biosynthesis inhibition in the host and fatty acid biosynthesis inhibition in *M. tuberculosis*. We feel so because *N. arbor-tristis* is rich in phytochemicals like iridoids,

flavonoids, etc. (Table 1) (Sah and Verma, 2012). It is also proved beyond any doubt that the phytochemicals mentioned above have lipid-lowering action in the host (Murti et al., 2012; Rathod et al., 2009). Crude extracts prepared from the flower and the root of *N. arbor-tristis* have already been reported to reduce cholesterol levels in the mice model (Rangika et al., 2015). Phytochemicals in *N. arbor-tristis* (e.g., iridoids, Aglycone Ag-NY1) can inhibit host cholesterol biosynthesis by inhibiting HMG-CoA reductase, the key enzyme for cholesterol biosynthesis. Therefore, *N. arbor-tristis*-derived phytochemicals can control the growth and survival of *M. tuberculosis* in human hosts by reducing host cholesterol. Some phytochemicals derived from *N. arbor-tristis* (e.g., arbortristoside A, B, C) may inhibit the fatty acid biosynthesis of *M. tuberculosis* by targeting fatty acid synthase (FAS II). In this context, flavonoids present in N. arbor-tristis deserve a special mention because flavonoids are known to inhibit the growth of *M. tuberculosis* by inhibiting bacterial fatty acid biosynthesis (Brown et al., 2007). Therefore, phytochemicals derived from the plant can target bacterial mycolic acid biosynthesis and exert bacteriocidal action. In simple words, we feel that *N. arbor-tristis* derived phytochemicals can be beneficial for tuberculosis by reducing host cholesterol as well as by inhibiting bacterial mycolic acid biosynthesis. This is a unique approach as far as our knowledge goes. The present methodology of tuberculosis control either works through the host immune system (Bacille Calmette-Guerin vaccine) or the bacteria (INH, Rifampicin, etc.). However, *N. arbor-tristis* derived phytochemicals can prevent and cure tuberculosis, acting both through the host and the bacteria. Additionally, the extracts of *N. arbor-tristis* are known for controlling hyperglycemia. Since diabetes mellitus is an established risk factor for tuberculosis, controlling glycemia in diabetic patients will also help prevent tuberculosis by the plant products. However, future *in vitro* and *in vivo* studies based on our hypothesis may be a step forward to take alternative and safe therapeutic strategies for managing tuberculosis patients.

Table 1. List of phytochemicals present in the *N. arbor-tristis* plant and their functions to inhibit fatty acid and cholesterol biosynthesis

No	Phytochemicals			Inhibitory roles in fatty acid/cholesterol biosynthesis	References
	Name	Source/Plant parts	Chemical class		
1	Arbortristoside A	Seed	Iridoid	Cholesterol and triglycerides lowering effect	Rangika et al., 2015; Rathod et al., 2009; Murti et al., 2012; Rani et al., 2012
2	Arbortristoside B	Seed	Iridoid	Cholesterol and triglycerides lowering effect	Rangika et al., 2015; Rathod et al., 2009; Murti et al., 2012; Rani et al., 2012
3	Arbortristoside C	Seed	Iridoid	Cholesterol and triglycerides lowering effect	Rangika et al., 2015; Rathod et al., 2009; Murti et al., 2012; Rani et al., 2012
4	Arbortristoside D	Seed	Iridoid	Not reported	-
5	Arbortristoside E	Seed	Iridoid	Not reported	-
6	Glycerides	Seed	Ester	Not reported	-
7	Lignoceric acid	Seed	Saturated fatty acid	Not reported	-
8	Stearic acid	Seed, bark	Saturated fatty acid	Reduce LDL cholesterol	Mensink, 2005
9	Palmitic acid	Seed, bark	Saturated fatty acid	Inhibitor of fatty acid synthesis in mammary tissue	Wright et al., 2002
10	Myristic acid	Seed, bark	Saturated fatty acid	Not reported	-
11	3-4 Secotriterpene acid	Seed	Amide conjugate	Not reported	-
12	D-Glucose	Seed, root	Carbohydrate	Not reported	-
13	D-Mannose	Seed	Carbohydrate	Not reported	-
14	Friedelin	Seed	Terpenoid	Not reported	-
15	Nycanthin	Flower	Terpenoid	Not reported	-
16	Flavonoids	Flower	Flavonoid	Inhibition of *in vitro* cholesterol synthesis, beta-ketoacyl synthase domain of FAS to inhibit the elongation of the saturated acyl groups in fatty acids synthesis.	Brown et al., 2007
17	Anthocyanins	Flower	Flavonoids	Not reported	-
18	Essential oil	Flower	Fatty acid	Not reported	-
19	β-Monogentiobioside	Flower	Carotenoid	Not reported	-
20	β-Digentiobioside	Flower	Carotenoid	Not reported	-
21	α-Pinene	Flower	Terpenoid	Inhibition of fatty acid synthesis	Aydin et al., 2013
22	*p*-Cymene	Flower	Terpenoid	Not reported	-
23	1-hexanol methyl heptanone	Flower	Ketone	Not reported	-
24	Phenylacetaldehyde	Flower	Aldehyde	Not reported	-
25	1-Deconol	Flower	Fatty alcohol	Not reported	-
26	Anisaldehyde	Flower	Aldehyde	Not reported	-
27	4-hydroxy hexahydrobezofuran-7-one	Flower, leaf	Flavonoids	Not reported	-
28	Rengyolone and its acetate NCS-2	Flower	Flavonoids	Not reported	-
29	Aglycone Ag-NY1	Tubular calyx of flowers	Carotenoid	Inhibit both the effect of HMG CoA reductase and acyl CoA: cholesterol *O*-acyltransferase activities.	Gebhardt, 1998
30	6β-Hydroxyloganin	Leaf	Iridoid	Not reported	-
31	D-Mannitol	Leaf, root	Carbohydrate	Not reported	-
32	β-Sitosterol	Leaf	Phytosterol	Not reported	-
33	Astragalin	Leaf	Flavonoid	Inhibit cholesterol synthesis in higher concentration	-
34	Nicotiflorin	Leaf	Flavonoid	Not reported	-
35	Oleanolic acid	Leaf	Terpenoid	Inhibit the fat production	-
36	Nyctanthic acid	Leaf	Terpenoid	Not reported	-
37	Tannic acid	Leaf	Polyphenol	Reduce total and LDL cholesterol in cholesterol-fed rats. Inhibit fatty acid synthase activity.	-
38	Ascorbic acid	Leaf	Vitamin	High concentrations of vitamin C inhibit the activity of HMG-CoA reductase *in vitro*.	Harwood et al., 1986
39	Methyl salicylate	Leaf	Glucoside	Not reported	-

No	Phytochemicals			Inhibitory roles in fatty acid/cholesterol biosynthesis	References
	Name	Source/Plant parts	Chemical class		
40	Volatile oil	Leaf	Fatty acid	Not reported	-
41	Friedeline	Leaf	Terpenoid	Lowering of lipid levels in plasma and liver	Duraipandiyan et al., 2016
42	Lupeol	Leaf	Terpenoid	Lupeol reduces triglyceride and cholesterol synthesis in human hepatoma cells	Itoh et al., 2009
43	Glucose	Leaf	Carbohydrate	Not reported	-
44	Calceolarioside A	Leaf	Verbascoside	Not reported	-
45	Naringenin-4'-*O*-β-D-glucopyranosyl-α-xylopyranoside	Stem	Flavonoid	Not reported	-
46	β-sitosterol	Stem	Phytosterols	Not reported	-
47	Iridoid	Bark	Terpenoid	Monoterpenes have been found to inhibit hepatic HMG CoA reductase by 50 to 60%	Middleton and Kok-Pheng, 1982
48	Phenylpropanoid	Bark, seed	Flavonoid	Inhibition of triglyceride (TG) synthesis and promotion of cholesterol catabolism.	Yang et al., 2015
49	Tannin	Root	Polyphenol	A low concentration of condensed tannins from catechu significantly inhibits fatty acid synthase.	Zhang et al., 2008
50	Caproic acid	Bark	Fatty acid	-	-
51	Nonanoic acid	Bark	Fatty acid	-	-
52	Capric acid	Bark	Fatty acid	-	-
53	Undecanoic acid	Bark	Fatty acid	-	-
54	Lauric acid	Bark	Fatty acid	-	-
56	Tridecanoic acid	Bark	Fatty acid	-	-
57	Myristoleic acid	Bark	Fatty acid	-	-
58	Pentadecanoic acid	Bark	Fatty acid	-	-
59	Palmitoleic acid	Bark	Fatty acid	-	-
60	Heptadecanoic acid	Bark	Fatty acid	-	-
61	Oleic acid	Bark	Fatty acid	-	-
62	Linoleic acid	Bark	Fatty acid	-	-
63	α-Linolenic acid	Bark	Fatty acid	-	-
64	Arachidic acid	Bark	Fatty acid	-	-
65	Eicosenoic acid	Bark	Fatty acid	-	-
66	Octadecatetraenoic acid	Bark	Fatty acid	-	-
67	Eicosadienoic acid	Bark	Fatty acid	-	-
68	Arachidonic acid	Bark	Fatty acid	-	-
69	Behenic acid	Bark	Fatty acid	-	-
70	Nyctanthin	Root	Alkaloid	-	-

11. Conclusions

The current treatment of tuberculosis mainly relies on the drugs such as isoniazid, rifampin, ethambutol, pyrazinamide (Yew et al., 2010; McIlleron et al., 2006). The choice of multi drugs is due to reducing both initial bacterial load and persisters. The first-line drug such as isoniazid can reduce the initial bacterial load by about 95% within the first two days (Joshi, 2011). Rifampicin is quite effective against the persisters during the initial failure of isoniazid due to resistant or sensitive strains. The period of these multidrug chemotherapies with a minimum of nine months to a maximum of eighteen months could be reduced to six months by adding pyrazinamide. Due to the failure of the first-line drugs, the second-line treatment could be prescribed for the period of eighteen to twenty-four months of prophylaxis. The extended prophylaxis of TB drugs often develops resistance mechanisms in tubercle bacilli due to certain mutational changes (Veen, 1995). Additionally, prolonged treatment with a higher concentration of TB drugs becomes toxic for internal organs like the liver, kidney, etc. (Saukkonen et al., 2006). Thus, there is a need to improve the therapeutic approaches by employing safe and effective drugs against the pathogenesis of *M. tuberculosis*. The present review indicates a specific and target-based approach against the pathogenesis of *M. tuberculosis*. There is evidence that iridoids, flavonoids, etc., obtained from different sources have potential lipid-lowering action (Khanna et al., 1994). Besides, based on different studies and reports, we believe that major phytochemicals obtained from the plant extract of *N. arbor-tristis* may also exhibit a similar mechanism of action (Debnath et al., 2012; Rangika et al., 2015; Rathod et al., 2009). The lipid-lowering action appears in the host and the bacteria, which is expected to have a profound antimycobacterial role. The anti-ulcerogenic, ulcer-healing properties and *in vivo* studies of these phytochemicals instigate us to further assess them as safe, non-toxic natural products (Ekeanyanwu and Njoku, 2014; Mishra et al., 2013; Rani et al., 2012). However, *in vitro* and in vivo studies are required in a large cohort in this regard. Further studies need to be conducted to explore the molecular interactions between *N. arbor-tristis* phytochemicals and *M. tuberculosis*, which may exhibit the target-specific inhibition of the bacterium. And we feel that validation of our hypothesis is urgently required since the modern world is facing a threat from multidrug-resistant tuberculosis, which demands exploration of novel strategies for effective prevention and control of tuberculosis.

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Conflict of interest

The authors confirm that there are no known conflicts of interest.

CRediT authorship contribution statement

Subendu Sarkar: Conceptualization, Data curation, Investigation, Writing-reviewing & editing the manuscript, Reviewing the manuscript
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Supplementary File

None.

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