Bioprospective Role of *Ocimum Sanctum* & *Solanum Xanthocarpum* against Emerging Pathogen: *Mycobacterium Avium* Subspecies *Paratuberculosis*

Manthena Navabharath; Shoor Vir Singh*; Garima Vashistha

Department of Biotechnology, Institute of Applied Science & Humanities, GLA University, Mathura, Uttar Pradesh.

**Abstract**

*Mycobacterium avium* subspecies *Paratuberculosis* (MAP) chronic, contagious and typically life-threatening enteric disease of ruminants caused by a bacterium of the genus *Mycobacterium* but can also affect non-ruminant animals. MAP transmission occurs through the fecal-oral pathway in neonates and young animals. After infection, animals generate IL-4, IL-5, and IL-10, resulting in Th2 response. Early detection of the disease is necessary to avoid its spread. Many detection methods viz., staining, culture and molecular methods are available and numerous vaccines and anti-tuberculosis drugs are used to control the disease. However, prolong use of Anti-tuberculosis drugs leads to the development of resistance. Whereas vaccines hamper the differentiation between infected and vaccinated animals in an endemic herd. This leads to the identification of plant-based bioactive compounds to treat the disease. Compounds of *Ocimum sanctum* and *Solanum xanthocarpum* have been evaluated to check the anti-MAP activity. Based on the MIC50 values Ursolic acid (32-64 µg/mL), Linalool (0.12%), Beta-caryollene (32 µg/mL), Propionic acid (0.25%), Rosmarine acid (1.2 µg/mL), Chlorogenic acid (20-80 µg/mL), Stigmasterol glucoside (0.67 µg/mL), cycloartanol (8 µg/mL), Stigmasterol (3.13 µg/mL), Beta-siyosterol (6.25 µg/mL) were found suitable to act as Anti-MAP.

**Keywords:** Bioactive compounds; *Mycobacterium avium* subspecies paratuberculosis (MAP); *Solanum xanthocarpum*, *Ocimum sanctum*; Ursolic acid.

**Introduction**

Johne’s disease in ruminants is caused by *Mycobacterium avium* subsp. *Paratuberculosis* (MAP), a persistent rubor with significant economic effects and global dissemination [1]. The apparent correlation between *Mycobacterium avium* subspecies *paratuberculosis* and Crohn's disease in individuals is still being studied extensively, with conflicting results [2-4]. In 1895, German researchers Johne and Frothingham acknowledged MAP for the first time [5]. It commonly infects ruminants (cattle, sheep, goats, deer, and so on) (Figure 1), however, it has also been reported in non-ruminants, notably wildlife [6]. Annual cattle sector losses in the United States have been estimated to be between $250 million [7] and $1.5 billion [8]. According to a new assessment...
of available data employing a Bayesian technique [9], calibrated for susceptibility and explicitness, the underlying frequency of MAP in dairy cattle in the United States was 91.1%, not 70.4% claimed in 2007 [10]. The incidence of MAP in beef cattle herds is 7.9% [11]. Even though JD was initially discovered in the United States during the early 1900s, the emphasis on investigation and disease prevention alone has expanded in the last 20 years. To combat Johne’s disease on a farm as well as to recognize herds having minimal infection susceptibility, a discretionary Bovine JD Management Program is in operation. The examination of ambient stool specimens via culturing through elevated sites is among the most cost-effective as well as highly reliable diagnostic techniques for JD [9]. Ironically, wildlife repositories may disrupt initiatives to reduce Johne’s disease in livestock unless their significance in wildlife is completely defined [13]. JD transmission is reduced when improved diagnoses are combined with good management strategies [12].

Taxonomy and properties

The Mycobacterium avium complex, which belongs to the genus Mycobacterium and the family Mycobacteriaceae, contains MAP. Mycobacterium avium and Mycobacterium intracellulare are two distinct species in the Mycobacterium avium complex. Mycobacterium avium subsp. avium, Mycobacterium avium subsp. hominissuis (MAH), MAP, and Mycobacterium avium subsp. silvaticum are the four subspecies of M. avium, according to a thorough sequence-based evaluation of the internal transcribed spacer of 16S-23S ribosomal RNA [14,15]. MAP is a gram-positive, acid-fast, rod-shaped intracellular bacteria with a diameter of 0.5 to 1.5 m. The bacterial cell wall is dense and waxy arabinogalactan holds the mycolate and peptidoglycan layers intact. Bacteria is a slow-growing that takes over 20 hrs. to multiply [16]. Efforts to build up MAP in the research lab medium were initially unsuccessful [17], and it was hypothesized that MAP’s failure to cultivate in-vitro was due to a scarcity of a crucial development factor. Further analysis revealed that MAP could flourish on a medium enriched with extracts from many other mycobacteria [18,19], leading scientists to assume that MAP cannot generate a vital growth factor that some other species can synthesize. Mycobactin is a siderophore that binds iron and is produced from Mycobacterium phlei, which has been identified as the growth factor required for MAP cultivation in-vitro [20,21]. Mycobactin dependence has been regarded as taxonomic for MAP since that period. A mission in the mbtA gene in the mycobactin-production operon has recently revealed a molecular knowledge of mycobactin reliance, as explained further below with the genome sequence [22,23].

Pathogenesis

Johne’s Disease (JD) is characterized by persistent diarrhea and a malabsorption condition, which results in malnutrition and muscle atrophy (Figure 2A). The faeco-oral pathway is the most common way for neonates and young animals to become infected. Milk feeding from infected dam is another source of infection to neonates [24]. Calves up to the age of six months have a greater incidence of infection, but afterward, the risk reduces [25]. According to animal research, M-cells and enterocytes both promote MAP adjunct to and transit through the gut mucosa upon consumption [26]. Tissue culture observations demonstrate that MAP influences the establishment of tight junctions in the intestinal mucosa, offering a mechanism for enhanced permeability [27] (Figure 2). Antigens 85 [28], 35 kDa [29], MAP oxidoreductase [30], MAP fibronectin-binding protein [31,32], and histone HupB [33] are all crucial in MAP epithelial cell adhesion and/or penetration, and there is a lot of host-pathogen interaction going on. Prior literature has shown that phagosome acidification stimulates interleukin (IL)-1 production, macrophage recruitment, and trans-epithelial migration in MAP-infected epithelial cells utilizing the cow mammary epithelial cell line MAC-T [34] and bovine Blood-Monocyte-Derived Macrophages (BMDM) [35]. Bacilli (genus Bacillus) are subsequently phagocytosed in the sub- and intraepithelial spaces by these macrophages [36-38]. For pathogenesis, MAP’s capacity to persist and proliferate once inside phagocytic cells is fundamental [39,40]. Furthermore, researchers observed that the lipid content of MAP changes in macrophages that acquire a pro-inflammatory phenotype utilizing a culture passage model (Figure 3) [41].

The pathognomonic granulomatous enteritis of Johne’s illness [38], which is characterized by a wide and ridged intestinal wall as well as inflammatory lymph nodes, is the result of the ensuing host cellular immunological response. Toll-like receptors help tissue macrophages and dendritic cells recognize molecular patterns linked with pathogens in the innate phase, as well as the abstraction of cytokine-mediated cellular connections and antigen processing [42,43]. In the acquired immunity phase, Th1 T-helper cell responses and concurrent stimulation of macrophages by Interferon-Gamma (INF) produced by Th1 T cells are used to reduce MAP infections [44,45]. The inferential function of nitric oxide synthase, has already been shown in cattle, is implicated in the killing process of these activated phagocytic cells [46]. In this condition, BMDM recovered from sub-clinically contaminated animals exhibits exceptionally high levels of nitric oxide generation (Figure 4) [47]. MAP, on the other hand, affects the activity of bovine macrophages, as demonstrated by distinct profiles of mRNA expression [48], apoptosis suppression and antigen distribution [49], and diagnostic cytokine expression patterns [50]. In infected bovine T helper cells, MAP mostly generates a Th2 response, with increased production of IL-4, IL-5, IL-10, and tissues remodeling inhibitors [51,52]. This humoral response was confirmed in a newborn calf model [53]. In addition, in both ruminants and animals, regulatory T and Th17 cells have been involved in the immune pathogenesis of JD [49,54].

MAP pathogenesis has been studied using a variety of models. MAP, on the other hand, produces immunological responses in ruminant hosts not found in traditional in vitro models. MAP bacilli grow during 4–8 days in infected BMDM [44,55], although bacterial burdens are reduced over time after infection of the murine J774 macrophage cell line [44,55-57]. When researching, the interactions between MAP and phagocytic cells, it is preferable to use primary phagocytic cells. To follow the progression of MAP infection from initial to final stages, Ileal loops have been employed to establish a prospective systems biology approach [58]. The host transcriptome profile following infection with M. avium subsp. avium and MAP were recently compared using this paradigm. Intestinal mucosal weakening, activation of a Th2 reaction, and phagocytosis suppression were all related to MAP transmission, which was not found with M. avium subsp. avium infection (Figure 5) [59].
**Diagnosis and control**

Before any clinical indications, infected animals shed MAP in their feces, making them a prominent cause of infection for the herd’s other animals. To avoid the spread of JD, it is critical to diagnose the infection as soon as possible. Based on the detection of MAP both directly and indirectly, many diagnostic tests have been created [60]. Direct identification of MAP in clinical specimens can be thriving using (i) microscopy, (ii) culture-based MAP isolation, and (iii) PCR-based MAP DNA identification. Clinical samples have been analyzed using acid-fast staining or Ziehl–Neelsen. Acid-fast staining is the easiest, quickest, and also the most economical mode of diagnosis, but its accuracy and precision are inadequate since it is challenging to discern between MAP and some other acid-fast bacilli [61]. Although Ziehl–Neelsen staining can also be used to screen for MAP; it must be verified by additional procedures such as PCR and/or immunoassays. The “gold standard” for JD diagnosis is MAP isolation through culture. The fact that MAP requires mycobactin J to grow in a specific laboratory medium can be utilized to distinguish it from many other acid-fast bacteria. A novel growth media that increases MAP restoration and sensitivity by 1,000-fold was recently divulged [62]. Because MAP develops slowly (On solid medium, colony development takes 6–8 weeks.), culture-based diagnosis takes a long period. As a consequence, a highly fast and precise PCR-based test was employed for MAP identification in environmental and clinical specimens [63-65]. IS900 is a 1.4 kb multi-copy insertion element that is sequence specific to MAP. The primers used in this PCR are for IS900 [60, 66]. Other mycobacteria with IS900-like insertion sequences, on the other hand, have been demonstrated to influence the specificity of this test, resulting in false-positive findings [64,67]. To prevent false-positive results, a multiplex PCR centered on the IS900, IS901, IS1245, and dnaJ genes was constructed, although the precision of this assay is restricted owing to reagent interference and primer-dimer generation [60, 68]. Furthermore, PCR tests based on stool specimens hold only 70% sensitivity and 85% specificity [69]. There has been some advancement in identify-
testing results [83]. Because JD is induced by a bacteria called
bile) that are currently being examined [81]. Eventually, to suc-
ing JD diagnostic testing [80], and strain 316F was created in the
cestor vaccination for JD in cattle. Unfortunately, since strain 18
hem immunity. In the United States, for instance, Mycopar®
ment systems used to have been applied to cure TB, going
paratuberculosis (Paratuberculosis) Indirect (ID Screen®
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AyurvedicName: Tulsi  
Division: Magnoliophyta  
Class: Magnoliopsida  
Subclass: Asteridae  
Order: Lamiales  
Family: Lamiaceae  
Genus: Ocimum  

Morphology  
*Ocimum sanctum* (Holy basil) is an upright, multi-branched sub-shrub, 300–600 mm (30-60 cm) tall with hairy stems. Leaves color is purple or green; the petioled, with up to 5 cm (2 inches) long and ovate blade and also a slightly toothed margin; the plant fragrant is very strong and Phyllotaxy is decussate. The flowers are purplish and placed in close whorls on elongated racemes [90]. In India and Nepal, three main types of morphotypes are cultivated that is Ram tulsi (which is a common type with broad bright slightly sweet green leaves). Purplish green-leaved is less common in Krishna or Shyamtulsi and Vana tulsi is the common in wild [91].

Soil and climate  
*Ocimum sanctum* (Holy basil) plant can be grown in moderately shaded conditions with low oil contents. Waterlogged conditions can cause root rot and growth to be stunted. It well flourishes under high rainfall and humid conditions. The high temperatures and long days have been found favorable for plant growth and oil production. Soil & Manure: Porous, aerated, and well-drained with added organic manure of soil is required for plant growth. Clay & Sticky soil is not good for the plant's roots.

Floral characteristics  
*Ocimum sanctum* plant is a short-lived perennial shrub or small annual, up to 3.3 feet (100 cm) in height. The simple toothed and hairy stems are oppositely entire leaves along with the stem. The scented leaves are purple or green, depending upon the variety. The white tubular or small purple flowers have green or purple sepal and are supported by terminal spikes. The nut-lets fruits and numerous seeds are produced.

Propagation  
*Ocimum sanctum* crop can be propagating through the seeds and sown in the nursery beds. 300 g of seeds are required in one hectare for the sowing. The nursery should be located in partial shade with sufficient irrigation facilities and soil depth up to 30 cm. well organic manure is applied to the soil and prepared to a seed beds size is 4.5 x 1.0 x 0.2 m. As seed quantity is mixed with the sand ratio is 1:4 required for sown in a nursery bed and 60 days advance in the onset of monsoon. The 8-12 days seeds can germinate and transplant seedlings in about 6 weeks during the 4-5 leaf stage.

Distribution  
The Holy basil plant is widely distributed throughout India and Central University of Punjab and Bathinda researchers have done research from the study of large-scale phylogeny graphical of this species using chloroplast whole genomic sequencing then team revealed that this holy basil plant originates from North-Central India [92].

*Ocimum sanctum* is a native herb in India, and also known as ‘Tulsi’ belongs to the family Lamiaceae. The Hindu religious tradition is sacred and is viewed as perhaps the most significant plant used in Ayurvedic medicine [93]. Tulsi plants grow in abundance around Hindu temples. Found in so many varieties strong like green and a red, pleasant aroma. In the previous decade several scientific shreds of evidence have been reported [94,95,96] at holy basil has been utilized to treat a variety of many critical diseases [97] including asthma, arthritis, heart problems, eye disorders, blood glucose levels, hepato protective, anticancer, anti-fungal,

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Bioactive constituents</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; Value</th>
<th>Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eugenol</td>
<td>500 μg/ml</td>
<td>Antifungal</td>
<td>Ahmad et al., 2015 [102]</td>
</tr>
<tr>
<td>2</td>
<td>Linalool</td>
<td>0.12%</td>
<td>Antimicrobial</td>
<td>Federman et al., 2016 [103]</td>
</tr>
<tr>
<td>3</td>
<td>Ursolic acid</td>
<td>32 μg/mL 64 μg/mL</td>
<td>Antimicrobial</td>
<td>Do Nascimento et al., 2014[104]</td>
</tr>
<tr>
<td>4</td>
<td>beta-caryophyllene</td>
<td>32 μg/mL 1024 μg/ml</td>
<td>Antimicrobial</td>
<td>Santos et al., 2021 [105]</td>
</tr>
<tr>
<td>5</td>
<td>Propionic acid</td>
<td>0.25% 0.125%</td>
<td>Antimicrobial Antifungal</td>
<td>Haque et al., 2009 [106]</td>
</tr>
<tr>
<td>6</td>
<td>Rosmarinic acid</td>
<td>1.2 mg/ml 0.3 mg/ml</td>
<td>Antimicrobial Antifungal Antiviral</td>
<td>Abedini et al., 2013 [107]</td>
</tr>
<tr>
<td>7</td>
<td>Apigenin</td>
<td>&gt;4 mg/ml</td>
<td>Antimicrobial</td>
<td>Nayaka et al., 2014 [108]</td>
</tr>
<tr>
<td>8</td>
<td>Orientin</td>
<td>500 μg/ml 1000 μg/ml</td>
<td>Antimicrobial</td>
<td>Karpiński et al., 2019 [109]</td>
</tr>
<tr>
<td>9</td>
<td>Isothymusin</td>
<td>200 μg/mL</td>
<td>Antimicrobial</td>
<td><a href="https://www.chemfaces.com/natural/Isothymusin-CFN97562.html">https://www.chemfaces.com/natural/Isothymusin-CFN97562.html</a> [110]</td>
</tr>
<tr>
<td>10</td>
<td>Vicenin-2</td>
<td>&gt;188μg/mL</td>
<td>Antimicrobial Antifungal</td>
<td>Mohotti et al., 2020 [111]</td>
</tr>
</tbody>
</table>
antimicrobial, chronic fever, anti-fertility and bronchitis [98,99] (Table 1) Ocimum sanctum have in so many chemical constituents such as carvacrol, eugenol, limatrol, linalool, ursolic acid, caryophyllene, propionic acid, methyl carvicol, Rosmarinic acid, Apigenin, cirsimaritin, Orientin, isothymusin and Vicenin [Figures S1, S2]. Previous research also showed that the Tulsi leaf juice shows complete growth inhibition of Anti-viral and Anti-Mycobacterial activities [100,101].

### Description of Solanum xanthocarpum Plant

**Taxonomic classification of Solanum xanthocarpum plant**

- **Scientific Name:** Solanum xanthocarpum
- **Ayurvedic Name:** Kantakari
- **Division:** Magnoliophyta
- **Class:** Magnoliopsida
- **Subclass:** Asteridae
- **Order:** Solanales
- **Family:** Solanaceae
- **Genus:** Solanum

### Morphology

Solanum xanthocarpum plant is a very thorny diffused bright green perennial herb, at the base is woody. Branches are several and spreading on the ground, the new branches are covered with dense stellate tomentum, yellow, straight, glabrous, prickles compressed, shining often exceeding and 13 mm long. Leaves are 50-100 x 25-57 mm, bearing stellate hairs on both sides of beneath, ovate or elliptic, Petioles are 13-25 mm long. Sometimes becoming nearly glabrous with age.

### Soil and climate

Solanum xanthocarpum is a hardy plant mainly grown in tropical and sub-tropical regions. It does adequately over light humus-rich, silty sand to rich loamy soils having pH of 7.0-8.0. Kantakari is a warm-season crop and also a crop grown over saline lands. The most favorable temperature range is 21-27°C for its growth and reproduction. Generally, abundant sunshine is required and dry weather with a long period of warm. In northern India, from December to January in this season the crop is adversely affected due to frost as it causes injury to vegetative parts and in the spring season plant will be recovered.

### Floral characteristics

Kantkari flowers are axillary bud, cymes and bluish-violet. The curved hairy stellate with short pedicels, linear-lanceolate, globose, prickly outside and lobes are 1.1 cm long. Purple Cololla, lobes deltoid, 20 mm long, acute, hairy outside. 1.5 mm long of Filament, 8 mm long of anthers, glabrous, oblong-lanceolate and tiny pores are opening. Style glabrous and ovary is ovoid. The berry-shaped fruits, 13-20 mm in diameter, are white or yellow with green veins and the calyx is enlarged. Seeds are 2.5 mm in diameter, sub-reniform, glabrous, smooth and yellowish-brown

### Distribution

Kantakari plant is widely distributed throughout India. The dry situation in the Himalayas as weed ascended to 1500 meters. Abundant by roadsides and wastelands, mainly in Uttar Pradesh, Rajasthan, Madhya Pradesh, Gujarat and Haryana.

### Propagation

The crop is elevated by seed and Yellowish-brown color in seeds, small size i.e. 0.25 cm in diameter and glabrous. There is no dormancy period for seeds and can be sown after some days

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**Table 2:** Biological mechanism between bioactive constituents with MIC values.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Bioactive constituents</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; value</th>
<th>Mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chlorogenic Acid</td>
<td>20 to 80 μg/mL</td>
<td>Antibacterial</td>
<td>Lou et al., 2011 [118]</td>
</tr>
<tr>
<td>2.</td>
<td>Stigmasterol glucoside</td>
<td>0.67 mg/ml</td>
<td>Antibacterial</td>
<td>Swain and Padhy et al., 2015 [119]</td>
</tr>
<tr>
<td>3.</td>
<td>3,4-dihydroxy cinnamic acid methyl ester</td>
<td>50-200 μg/mL</td>
<td>Antibacterial</td>
<td>Hua Du1 et al., 2009 [120]</td>
</tr>
<tr>
<td>4.</td>
<td>Solasodine</td>
<td>62.5 μg/mL</td>
<td>Antibacterial</td>
<td>Sinani and Eltayeb et al., 2017 [121]</td>
</tr>
<tr>
<td>5.</td>
<td>Solanine</td>
<td>240 μg/mL</td>
<td>Antifungal</td>
<td>Kumar P et al., 2009 [122]</td>
</tr>
<tr>
<td>6.</td>
<td>Cycloartanol</td>
<td>8 μg/mL</td>
<td>Antibacterial</td>
<td>Woldemichael et al., 2004 [123]</td>
</tr>
<tr>
<td>7.</td>
<td>Stigmesterol</td>
<td>3.13 μg/mL</td>
<td>Antibacterial</td>
<td>Mailafiya et al., 2018 [124]</td>
</tr>
<tr>
<td>8.</td>
<td>Beta-Sitosterol</td>
<td>6.25 μg/ml</td>
<td>Antibacterial</td>
<td>NWEZE et al., 2019 [125]</td>
</tr>
<tr>
<td>9.</td>
<td>Apigenin</td>
<td>&gt; 4 mg/mL</td>
<td>Antibacterial</td>
<td>Nayaka et al., 2014 [126]</td>
</tr>
<tr>
<td>10.</td>
<td>Esculestin</td>
<td>192 mg/mL &lt;0.015625 μg/mL</td>
<td>Antibacterial</td>
<td>Pushpanathan M et al., 2013 [127]</td>
</tr>
<tr>
<td>11.</td>
<td>Esculin</td>
<td>2500 mg/L</td>
<td>Antibacterial</td>
<td>Mokdad-Bzeouich et al., 2014 [128]</td>
</tr>
<tr>
<td>12.</td>
<td>Scopoletin</td>
<td>50 μg/mL (without sorbitol) &gt;200 μg/mL (with sorbitol)</td>
<td>Antifungal</td>
<td>Lemos et al., 2020 [129]</td>
</tr>
</tbody>
</table>
of harvesting. The germination percentage is around 60-70% and it will take 10-15 days to germinate.

_Solanum xanthocarpum_ is a native herb of India, and also known as kantkari belongs to the family Solanaceae. It is a thorny, bright green, perennial plant with woody roots that grow to a height of 2 to 3 meters and is found all over India, primarily in arid regions as a weed on highway shoulders and waste lands. The 1.3 cm in diameter, yellow or white berry with green veins, and expanded calyx-shaped fruits are produced [112]. In the previous decade much scientific evidence has been reported [113] at kantkari has been utilized to treat a variety of many critical diseases including cough, fever, heart diseases, antipyretic, hypotensive, antiasthmatic, antitumor, anti-anaphylactic, aphrodisiac activities, wound healing, anti-inflammatory, urinary bladder, laxative [114], blood glucose levels, hepatoprotective, anticancer, antifungal, antimicrobial, chronic fever, antifertility and bronchitis [115] (Table 2) _Solanum xanthocarpum_ have in so many chemical constituents such as chlorogenicacids, stigmasteryl glucoside, glucoalkaloidsolanocarpine, isochlorogenic, carpesterol, methyl ester of 3,4-dihydroxycinnamic acid,neochlorogenic cholesterol, 3,4-dihydroxycinnamic acid (caffeic acid), solanine-S, solasodine, Quercetin 3-O-D-Glucopyranosyl-(1,6)-D-Glucopyranoside, solasonine, Sitosterol-beta-D-Galactoside, solasurine, solamargine, cycloartanol, sitostereryl-glucoside, campesterol, stigmasterol (fruit); sitosterol, flavonal glycoside, apigenin (flower); amino acids and solanocarpine (seeds); esculetin, coumarins, esculin, scopolin and scopolitin (leaves, fruits and roots); norcarpesterol, tomatidenolandcarpesterol (plant) [116] (Figures S3, S4, S5). Previous researches also showed that the kantkari fruit juice show complete growth inhibition of Anti-viral (HIV), anticancer and Anti-Mycobacterial activities [117].

![Figure 1](https://example.com/figure1.jpg)
**Figure 1:** Structures and IUPAC names of 1-9 bio molecules of _Ocimum sanctum_ plant.

![Figure 2](https://example.com/figure2.jpg)
**Figure 2:** Structures and IUPAC names of 10-12 bio molecules of _Ocimum sanctum_ plant.
Natural chemicals can be utilized to enhance the efficacy of anti-tuberculosis treatments and perhaps fill in the gaps where regular prescription therapies have lost their effectiveness. Prevention and treatment strategies, combined with natural substances, may be a feasible alternative for reducing drug resistance. As discussed, natural substances possess a multitude of antimycobacterial characteristics and focus on several therapeutic targets. For instance, natural compounds can augment the sensitivity of mycobacterium to antibiotic treatment. Natural items should be researched further for the treatment of active TB. It is worth noting that many of the studies included in this review were carried out using techniques such as molecular assays, mouse models, animal cells, and bacterial culture. Natural products must be of excellent quality, authentic, well formulated, regularly derived from their sources, and not contaminated with other products. Novel natural chemicals are being researched in the hope that they will be effective in treating tuberculosis infections.

We emphasize on identifying plants based on ethnomedical complaints and testing their extracts/phytomolecules against My-
cobacterium paratuberculosis strain. In conclusion, we tried to give brief idea about those natural compounds found suitable to paraphrase research activity against paratuberculosis. In a result we can say that two plants extract can achieve good combination effect, although any antagonistic effect was not determined yet. Therefore, targeting these two agents will help in future to shorten the current therapeutic regimens for para TB and also for treating other tuberculosis diseases also.

Conflict of interest: There is no conflict of interest to declare.

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