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**Review Article**

# Versatile Use of Mycobacterium indicus pranii (MIP) Vaccine

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Mycobacterium indicus pranii (MIP) earlier known as Mw is a soil-borne, non-pathogenic, saprophytic and rapidly growing strain of mycobacteria. MIP is approved as a vaccine/ immunomodulator for various indications including mycobacterium infections like leprosy in humans. Its administration has resulted in satisfactory clinical improvement, accelerated bacillary clearance, and increased immune responses to *Mycobacterium leprae* antigens, thereby shortening the full recovery time of the patients. It also shares its antigens with *M.tuberculosis*. In the last decade, RCTs have been done establishing immunotherapeutic properties of MIP in the treatment of leprosy, tuberculosis, warts and experimently in leishmaniasis. Through its immune inducing and cytotoxic property, it has also proved beneficial for human use especially in treating lung cancer. The beneficial role of it is also being explored in breast, cervical, oral, liver, and bladder cancers. Various studies on MIP have shown that it has immune-modulating properties in humans. The curiosity of the human mind has led to it being tried in Covid treatment trials. The results have shown that administering MIP has lowered inflammatory markers in Covid 19 patients, promising us for it to be a potential treatment option. More RCTs with a larger sample size should be done to establish this. Cytokine storm seen in bacterial sepsis is also decreased with MIP administration. Considering the encouraging results in hastening recovery in various diseases it appears that MIP is perhaps not being exploited to its fullest potential.

**Key Words :** Mycobacterium indicus pranii, MIP, Mycobacterium w, Mw, Immunotherapy, Covid 19, Leprosy, Tuberculosis, Immunomodulator

## Introduction

Leprosy (Hansen's disease) is considered as among oldest known diseases to mankind. It is caused by *Mycobacterium leprae* and a variant known as *Mycobacterium lepromatosis*. About 95% of people who get infected with this acid-fast

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bacillus do not develop any disease. However, in affected people, it can damage nerves and lead to permanent disability. Therefore, it is still a public health challenge. Due to Multidrug therapy (MDT), the global leprosy burden dramatically fell from 54 lakhs cases in the 1980s to fewer than 2 lakhs cases in 2015. India reported 1.25 lakhs new infections in 2015-2016 (Thangaraju et al 2018a). Many more cases will be detected with campaigns like LCDC (Thangaraju et al 2018b). But the true numbers may be much higher. National leprosy eradication programme (NLEP) reported that 4.7 new leprosy cases per 100,000 population were recorded annually (NLEP 2021). Totally, 202,256 cases of leprosy positive were observed in the year of 2019 as per the WHO (WHO 2019). The data announced by WHO in 2019 of leprosy cases are considered as standard criteria for assessing the progress concerning to reach targets of NTD Roadmap 2030 and Global Leprosy Strategy 2021-2030. Therefore, development of vaccines for preventing disease and transmission should be our priority. Many vaccines have been tried for leprosy. MIP is now being considered by the Government of India for the prevention of leprosy and pilot studies are underway to understand the operational aspects. Mycobacterium indicus pranii (MIP) or conventionally known as *Mycobacterium w* (M.w) is a distinct mycobacterium species. This vaccine works by inducing $CD4^+$ T helper 1 (Th-1) cells to release cytokines like IL-2, IL-12, IL-15 and IFN-γ thereby promoting hosts cell-mediated immunity (Fig. 1). Combining chemotherapy and immunotherapy with MIP vaccine in leprosy patients resulted in faster recovery rates in the patients. On histopathological examination, complete granuloma clearance was also seen. During the last decade, the immune-modulating properties of this organism in humans have

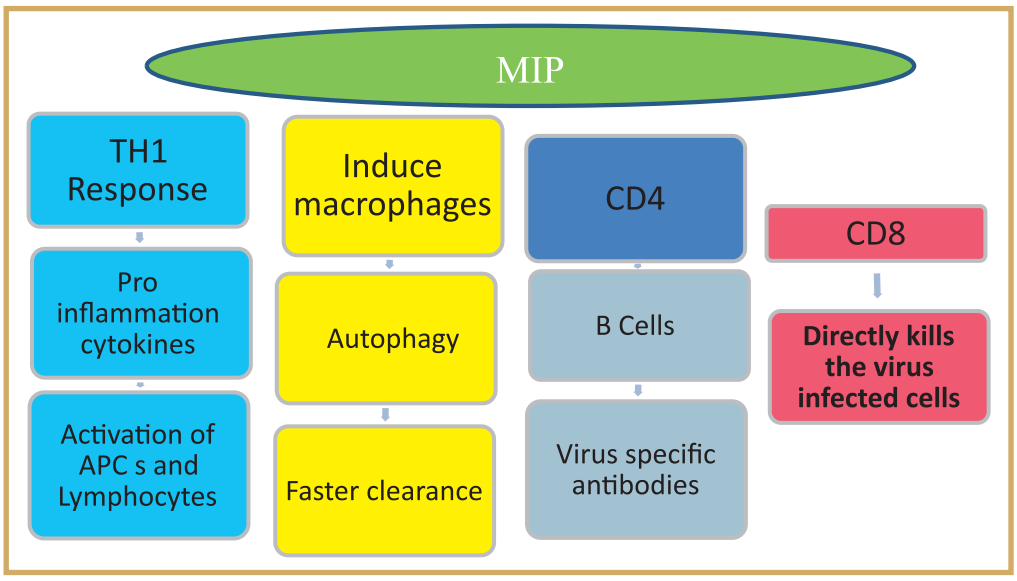


**Fig 1 : Proposed mechanism of action of MIP in host.**

been explored and the results turned out to be promising. It induces survival, activation of dendritic cell, Th1/Th17 polarization potential in a TLR-dependent manner. It also decreases the cytokine storm seen in the pathogenesis of COVID, bacterial sepsis (Subramaniam et al 2016). Various studies on MIP showed that it has some immune-modulating properties in humans (Halder et al 2017).

This article aims to highlight various current and potential uses of MIP vaccine/ immunomodulator.

**History of development of MIP and its application as vaccine/ immunomodulator:**

Mycobacterium indicus pranii (MIP) earlier known as Mycobacterium w is a saprophytic bacterial species originally identified by Prof GP Talwar and collaborators in 1978 (Talwar 1978) shares potential antigens with *M. leprae* and *M. tuberculosis*. On the basis of the evolution the organism has been reported to be the progenitor of *M. avium* complex but a distinct mycobacterium (Talwar 1999, Ahmed et al 2007, Saini et al 2009). Talwar et al in only 90's reported the results of comprehensive trial on the autoclaved inactivated MIP as Immunotherapeutic agent (vaccine) for the to control the infection in multibacillary leprosy patients (Talwar et al 1990). During the similar period other vaccine candidates such as armadillo grown and killed *M. leprae* and/ or in combination with BCG was employed by Convit et al for their immunoprophylaxis and immunotherapy towards the leprosy treatment and prevention (Convit et al 1982, Convit & Ulrich 2000). ICRC bacillus described by Bapat (Deo et al 1983), several others like *M.vaccae* (Stanford et al 1990), *M.habana* etc were reported to be useful for similar purpose (Kartikeyan et al 1991). MIP is proposed as a good candidate as a broad spectrum immunomodulator. It was initially considered as prospective vaccine towards leprosy due to various immunological properties. And it represents the indigenous vaccine from India originating not only as selective vaccine towards the mycobacterial infections but also it modulates the innate immune response hence proposed as adjunct vaccination component for many other immunotherapeutic applications for leprosy, tuberculosis, sepsis, HIV/Covid 19, warts, cancers etc. (Talwar et al 1990, Katoch et al 1995, Sur & Dastidar 2003, Sharma et al 2005, Gupta et al 2008, Sehgal et al 2015, 2020 & 2021, Singh et al 2014, Belani et al 2017, Sharma et al 2017, Kaur et al 2021).

Though many researchers are in the march of studying the disease pathology, many socioeconomic and political issues, yet the most important yardstick is the practical application of the vaccine candidates to reach the targeted population. Further the very slow growth of pathogens like leprosy bacillus results in long time to conduct the vaccine trials and commercialize (Ali 2020). MIP being fast growing mycobacterium and sharing crucial cross-reacting antigens makes it a very versatile candidate for the inducing the immune response against *M. leprae.*

Immunotherapeutic and immunoprophylactic usefulness of MIP has been discussed in the subsequent sections and paragraphs.

**Role of MIP in infectious diseases**

*Mycobacterium indicus pranii* (MIP) /Mw has immunomodulatory role in mycobacterial diseases possibly because of sharing of important antigens with *M. tuberculosis* and *M. leprae* (Guleria et al 1993, Talwar 1999, Saini et al 2009). It has also been shown to have generalized immunomodulatory action thus making it useful for many other infectious diseases including HI, Covid 19 infection (Talwar 1999, Kharkar 2002, Rakshit et al 2012, Sehgal et al 2020 & 2021a, Jaiswal et al 2021). Following part of this section deals with the role of MIP in various infectious diseases.

**MIP in Leprosy**

It was an important historical milestone when on January 30, 1998, a leprosy vaccine based on Mycobacterium w was released for public use for therapeutic purposes (Talwar 1999). After completion of phase III immunotherapeutic studies as an adjunct to drug therapy in urban and rural leprosy control centers it has been approved for industrial manufacture by the Drugs Controller of India. M/s Cadila Pharmaceuticals was given permission for its manufacture and distribution.

The major bottleneck in the development of vaccine based on *M. leprae* has been its non-cultivability in *in-vitro* media and also non-availability of animal host, the only host known is nine-bended armadillo. Because of these limitations Talwar & colleagues as well other collaborators (different studies published in 1977-78) screened various mycobacteria to identify antigenically cross-reactive cultivable mycobacterial species and Mw emerged as an important candidate (Talwar 1978). Stanford et al (1990), Deo et al (1983) and others pursued strains identified by them (Kartikeyan et al 1991). Among the strains sharing cross-reactive antigens, the potential of Mw (now MIP) was also recognized by others (Nath 1998).

Talwar and colleagues made persistent efforts in developing the Mw/ MIP as vaccine to leprosy. Extensive studies were conducted to evaluate the vaccine as well as immunotherapeutic efficacy and the results showed that the immunotherapy combined with the chemotherapy led to bacillary clearance and clinical recovery. Initially the studies were on the effect of multidrug therapy (MDT) comprising of Rifampicin, Clofazimine and Dapsone (DDS) in highly bacillated cases for minimum two years followed by MDT plus immunotherapy with Mw. Even though, the two years of treatment could not significantly reduce the bacillus index (BI) in bacilliferous leprosy cases, these cases showed lepromin conversion and enhanced bacterial clearance after immunization with Mw. In this context, these studies were an important milestone to prove the efficiency of MIP immunotherapy as an adjunct to MDT in clinical Phase-II trials. In these studies no adverse systemic adverse effects were observed after the vaccination in the vaccinated persons. M.w was found to be effective as immunotherapy with chemotherapy in bacillated cases - Mw repeated in three months (Talwar et al 1990, Zaheer et al 1993, Kar et al 1993, Sharma et al 2000, Sarkar et al 2001) or at six monthly intervals (Katoch et al 1995). According to a 2017 study by Kamal et al (2017), adding MIP vaccine to standard MDT in borderline leprosy patients also resulted in better clinical outcomes. Overall, combined chemotherapy and immunotherapy with Mw was found to be result in faster clinical recovery, faster bacillary killing and clearance, faster granuloma clearance (Natrajan et al 1992) and an overall decreased incidence of lepra reactions. MIP was also observed to have a significant immunoprophylactic role in household contacts of leprosy patients (Sharma et al 2005). After analysing the beneficial results various Mw trials, adding Mw/*Mycobacterium indicus pranii* vaccine into multidrug therapy in newly diagnosed leprosy cases for better treatment outcomes and immunoprophylaxis in contacts as leprosy control strategies for India's National Leprosy Eradication Programme have been recommended as a cost effective approach for eradication of leprosy (Muniyandi et al 2021).

**MIP in Tuberculosis**

Mw/MIP was initially shown to be effective against tuberculosis in experimental animals (Singh et al 1991, Guleria et al 1993). Katoch et al (2008) evaluated the protective efficacy of the MIP vaccine in the rural population of 28,948

people from 272 villages in Ghatampur, Kanpur (India). Originally, the population was vaccinated with two doses of Mw 10-13 years ago to assess its impact against leprosy (1st dosage of $1x10^9$ heat dead organisms followed 6 months later by a 2nd dose of $5x10^8$ organisms). In this study, the incidence and prevalence of pulmonary tuberculosis were determined in a blind manner by an active field survey as well as retrospectively by the patient's history of anti-tuberculosis treatment received in the intervening period (since vaccination), which was also confirmed by reviewing medical records. During the study, 69 patients with pulmonary tuberculosis were discovered, including 17 new sputum smear positive cases and 52 previously partially treated but still active pulmonary tuberculosis cases. There was a significant difference in new sputum positive cases between the vaccinated (5/17) and placebo (12/17) groups. Because 75% (52/69) of the cases were diagnosed with pulmonary tuberculosis but did not receive sufficient treatment, all cases identified during the interim period were recorded and re-analyzed. Only 12.85 percent of the contacts in the study population (total number=3036) showed BCG scars. On the basis of the data on tuberculosis protection in this group, it was also inferred that BCG did provide tuberculosis protection ($p<0.01$). The prevalence of tuberculosis was 1.11 percent in the placebo group, while it was 0.70 percent in those who received Mw vaccination (p 0.01), and 0.53 percent in those who had BCG scars and received Mw. These findings imply that Mw has protective activity against pulmonary tuberculosis and that it should be investigated in future prospective immunoprophylactic trials for pulmonary tuberculosis protection (Katoch et al 2008).

In experimental animals also, Mw/MIP vaccination was observed to be effective in accelerating the bacterial death and improving organ pathology when used in conjunction with chemotherapy. MIP treatment increased the amount of activated antigen-presenting cells and lymphocytes in infected lungs, as well as modulating the granulomatous response. In the immunotherapy group, there was an early increase in protective Th1 immune response. Following consecutive doses of MIP, there was a decrease in inflammatory response and an increase in immunosuppressive response, resulting in improved lung pathology (Gupta et al 2012 a, b).

Patel & Tripathy (2003) have tried Mw as immunotherapeutic and adjunct to anti-tuberculosis treatment (ATT) and observed that it improves cure rate. Afterwards, a multicentric clinical and randomized trial to assess the role of *Mycobacterium indicus pranii* (MIP) as an adjunct to anti-tuberculosis treatment (ATT) in 890 relapsed sputum smear-positive pulmonary TB patients, treatment failures and patients who are receiving ATT after interruption of treatment [earlier called Cat II pulmonary TB (PTB) patients] has been conducted (Sharma et al 2017). In this study intradermally 6 doses of heat-killed MIP or placebo once in 2 weeks for 2 months after randomization was given. After the 4th week, 67.1% of patients of the MIP group achieved sputum culture conversion compared to 57% of the placebo group (P=0.0002) (Sharma et al 2017). There were no adverse effects of MIP too. This data shows that MIP aids in bacillary clearance. Quicker the bacillary clearance, the lesser the chances of dissemination, and the better the prognosis. MIP thus has also the potential of being used as an adjunct to ATT to decrease the treatment duration thus indirectly increasing patients' compliance to therapy. Improved compliance will reduce the incidence of complications and the emergence of drug-resistant TB.

In another study, Mw (MIP) as adjunct immunotherapy increased the effect of pro-inflammatory cytokines (such as IFN-gamma, IL-2, IL-12, and TNF-alpha) while decreasing the production and effect of anti-inflammatory cytokines (like IL-10 and TGF-alpha), indicating (that subject to rigorous testing by other parameters, Mw (MIP) as adjunct immunotherapy has potential for reducing treatment duration (Chahar et al 2018). Immunization with MIP intranasally (Gupta et al 2019) caused recruitment of CD4+ and CD8+ into the lung airway lumen. T regulatory cells have been shown to be important in protection against tuberculosis in experimental animals (Das et al 2015). Also, T memory cells induced by MIP act as sentinels and enhance protection against infection of tuberculosis (Gupta et al 2019).

MIP when given subcutaneously or via aerosol route has shown to increase immune response produced by BCG. However, aerosol route proved to be more effective (Nagpal et al 2019).

**MIP in COVID 19 both as vaccine and adjuvant for therapy**

MIP is widely recognized for its immuno-modulatory functions. Not only MIP has ability to activate the cell mediated immune response against mycobacterial infections, but its generalized immunomodulatory action has expanded its applications as adjunct vaccine component for many other infectious diseases including HIV (Talwar 1999, Kharkar 2002, Rakshit et al 2012).

MIP is an effective agonist for the TLR2 (Pandey et al 2012, Kumar et al 2019) as well as it acts as a poly antagonist for TLR4, 5, 7, and 9. Most importantly it plays a role in p38 down regulation which consequentially induces the production of IL-2, IL-6, TNF-α, and IL-1b cytokines. And MIP is a competitor for the receptor of TRL4 which inhibits the cytokine production pathway at downstream level and reduces the various cytokines production. MIP is an efficient inducer of Th1 response, and several clinical trials proved that it is safe for human use especially with immunocompromised persons. It has been shown that the cell wall fraction of MIP induces the Th1 response as adjuvant (Saqib et al 2019). MIP increases the induced macrophages level when injected through intradermally (Kumar et al 2014a). TLR2 agonist property of MIP strongly stimulates the dendritic cells leads to the reduction in viral load (Kumar et al 2015).

MIP has been evaluated both as an immunoprophylactic (Kanani et al 2021) as well as also as an immunotherapeutic in Covid 19 (Sehgal et al 2020, 2021b; Jaiswal et al 2020, 2021) and beneficial effects have been reported.

Protective effect of MIP against Covid 19 has been studied - out of 96 health care workers 32 were administered a single dose of 0.1 ml of MIP and the remaining age-matched 64 HCW's were put in the control. 31 out of 96 developed RT PCR confirmed Covid-19 within 100 days. Despite significant exposure risk only one of the 32 HCW's who received MIP developed PCR confirmed Covid-19 i.e., approximately 94% protection rate (Jaiswal et al 2020, 2021). If this is re-established by large RCT's then the efficacy of giving MIP along with suboptimal doses of COVID vaccine should be analysed. And if this combination of co-vaccination turns out to be fruitful then the dose requirement of COVID vaccine especially in high-demand countries would be drastically reduced, thus making it possible to vaccinate a large population in lesser time.

Another clinical study described that MIP contributes to an early clinical recovery and improvement of dysfunction organs with increased Sequential Organ Failure Assessment (SOFA) score (Sehgal et al 2020). The same

situation could be applicable to COVID-19 patients those admitted in ICU with critical conditions and its related complications (Sehgal et al 2021a). A recent study performed in India have been examined that the improvement in C-reactive protein progressively and avoided the mechanical ventilation usage those patients who administrated intradermally with MIP. Additionally, there was no adverse effect report of MIP so far, it examined against COVID-19 patients having mild to moderate and critically health illness (Sehgal et al 2021a). Ingale et al (2021) also reported similar beneficial effects of use of MIP in Covid 19 cases. Patel et al (2021) used MIP intravenously and observed that this led to decreased oxygen requirement in critically ill patients.

The role of MIP has already been studied in decreasing the inflammatory markers in COVID 19 patients after its administration in the host. This means it has the potential to stop the progression of COVID 19 Pneumonia especially in nonhealing/deteriorating patients and hasten the recovery time. This has been confirmed by the observational study conducted by Ingale et al (2021) - 116 of 117 RT-PCR confirmed patients when given 0.3ml MIP intradermally for 3 days were discharged within 10 days of admission to the hospital. This report was shorter time than WHO's average recovery time which was 2 weeks for mild cases and 3-6 weeks for severe cases. A 40 member RCT by Dr. Suparno Chakrabarti to assess the response of memory NK cells in which 0.3ml was introduced intradermally for 3 days in critically ill Covid patients and 0.1ml of it on day 1 and day 30 in HCW's and close contacts is under progress. (CTRI/2020/10/028326).

Above studies suggest that usage of MIP is likely to result in quicker recovery and decreased viral load. Quicker recovery should be preferred because prolonged isolation has shown to affect patient's mental health too. Thus MIP could be used as a powerful adjuvant and Immunomodulator for the COVID-19 treatment for the faster recovery of the patients.

**Role of MIP in other diseases**

**(a) MIP in Leishmaniasis treatment**:

Visceral leishmaniasis (VL) caused by protozoan *Leishmania donovani*, is associated with a high fatality if left undiagnosed and untreated. The drugs– Sodium stibogluconate meglumine antimonite, Miltefosine, and Amphotericin B which are used in treating and are toxic and as a result, lead to non-compliance and emergence of drug-resistant strains. The situation becomes, even more, worse when there is co-infection of Leishmania and HIV. It is almost untreatable. Therefore, alternative therapy should be explored. Chemo immunotherapeutic approach with a combination of MIP (here acts as an immune stimulator) and Amphotericin B in treating visceral leishmaniasis has been demonstrated in BALB/c mice. This crosstalk between MIP and Amphotericin B combats the Leishmania parasite-induced host immune suppression. In a study conducted by Adhikari et al (2012b) when leishmania infected macrophages were treated with $10^7$ cells/ml of MIP, 72% parasitic clearance was achieved in 48 hours post-infection. And when this dose of MIP combined with a suboptimal dose of Amphotericin B [0.1 µg/ml] was used 96% parasitic clearance was achieved. Thus, it was possible to achieve good parasitic clearance by only using sub-optimal doses of MIP and Amphotericin B when both of them were combined. This combination is superior because both Amphotericin B and MIP at regular doses are somewhat cytotoxic. Adhikari et al (2012a) have also

demonstrated that the MIP and Amp B act by enhancing nitric oxide production which is considered to be toxic to the protozoan] by Leishmania-infected macrophages. MIP also promotes Th1- cytokine response and also up regulates production IL12 mimicking the host's response against the protozoan. However, MIP failed to clear parasites from the IL12 deficient host macrophages. These *in-vitro* and *in-vivo* observations need to be pursued further if MIP is to be considered as adjunct immunotherapeutic agent to treat leishmaniasis patients specially those having drug resistance.

**(b) MIP in treatment of Cutaneous Warts**:

Warts are caused by the viral infection with human papilloma virus (HPV). The role of intralesional injection of MIP in extragenital warts has been studied by several investigators. In a study on 44 patients complete clearance was achieved in 55% of patients with 3 to 4 intralesional doses of MIP whereas in 84% of subjects cosmetically acceptable response was achieved (i.e. greater than 75% clearance). However, about 80% of patients experienced mild therapy-related side effects. Singh et al (2014) also reported promising results and opined that larger RCT should be done to ascertain its role in the treatment of ano-genital and cutaneous warts as compared to standard therapies (Singh et al 2014). Another study was conducted on intralesional MIP vaccines with wart and found that the minimum of 0.186 ml as a dose was required for the treatment of subungual and periungual wart. Among the all the patients, 93.33% of the patients were completely recovered at injected and distant sites (Garg & Baveja 2014). An early (9.41 vs. 11.71 weeks) and significantly higher response (90 percent Grade 4 vs. 76.67 percent Grade 4) were found in a trial comparing MMR and MIP vaccines in the treatment of cutaneous warts ($P< 0.05$). Beneficial effects have also been reported by others in the treatment of warts (Gupta et al 2008, Kumar et al 2014b). Furthermore, it was justified that because MIP vaccine is a dead vaccine, it may be beneficial to people who are immunocompromised or for whom live vaccinations are not recommended (Kaur et al 2021).

**(c) Role of MIP in Sepsis:**

MIP has been studied as immunomodulator in the management of severe cases of sepsis. Results have been quite good (Sehgal et al 2015, 2021b) and its use as Sepsivac has been shown to improve the response to therapy in sepsis**.**

(d) **MIP and Cancer:**

Regarding the usefulness of MIP as an adjuvant in anticancer therapy many experimental (Ahmad et al 2011, Kumar et al 2019) as well pre-clinical /clinical studies have been reported during the last two decades (Sur & Dastidar 2003, Sarkar & Dasgupta 2005, Belani et al 2017, Om Parkash et al 2018). Beneficial effects of use of MIP in the therapy in human trials have been reported, these include lung cancer (Sur et al 2003), head & neck cancer (Sarkar & Dasgupta 2005, Om Parkash et al 2018), bladder cancer (Chaudhuri & Mukhopadhaya 2003). Applications include its usefulness as adjuvant as well as its role in palliative management.

**Adverse effects with use of Mw -MIP:**

MIP has been generally found to be safe. Besides local injection issues, no serious effects have been reported in more than three decades of its use

**Table 1 : Experimental and clinical use of MIP in various diseases.**

| S. No. | Treatment | Human/ Experimental Animals | Dosages | Frequency | Route of administration | References |
|---|---|---|---|---|---|---|
| 1 | Anticancer Lung cancer | Human | - | - | - | Sur & Dastidar 2003 |
| 2 | Anticancer Head & neck cancer | Human | 0.2 ml | Weelkly once 6 doses | Intradermal | Sarkar & Dasgupta 2005, Om Parkash et al 2018 |
| 3 | Anti-tumour Bladder cancer | Human | - | - | - | Chaudhuri & Mukhopadhaya 2003 |
| 4 | Adjunct to Anti-tubercular treatment | Human | $5\times10^8$ bacilli or placebo | Once in 2 weeks for 2 months | Intradermal | Sharma et al 2017 |
| 5 | Tuberculosis | Mice | 200 CFU of aerosolized | 2 doses at 3 weeks intervel | Intranasal | Gupta et al 2019 |
| 6 | MIP Immunotherapy as an Adjunct to Chemotherapy for Tuberculosis | Guinea pig | $10^5$ bacilli in 100 µl | 5 doses (every 15 day) | Subcutaneous | Gupta et al 2012 |
| 7 | Anogenital Warts | Human | Vehicle cream and intralesional Mw vaccine | - | Intralesional | Kumar et al 2014b |
| 8 | MDT + MIP vaccination for treatment of leprosy along with immunization of contacts | Human | Review of different studies | Six monthly/ 3 monthly repeat doses | Intradermal | Muniyandi et al 2021 |
| 9 | MDT + MIP vaccination for leprosy | Human | $5 \times 10^8$ killed bacilli | Two injections initially and then single dose every three months | Intradermal | Talwar et al 1990, Kar et al 1993, Zaheer et al 1993 |
| | | | | Six monthly injections | | Katoch et al 1995 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 | Sepsis | Human | 0.1ml -0.5x$10^8$ | 0.3ml divided in three doses in three sites for 3 days | Intradermal | Sehgal et al 2015, 2021b |
| 10 | COVID-19 | Human | 0.1ml of 0.5×$10^8$ heat killed x3 each day | Three consecutive days | Intradermal | Sehgal et al 2021 |
| | | | 0.6 ml | | Intravenous | Patel et al 2021 |
| 11 | COVID-19 | Human | 0.3 ml | Three consecutive days | Intradermal | Ingale et al 2021 |
| 12 | Visceral Leishmaniasis | Mice | $10^8$/100 µl | Single dose | Intravenous | Adhikari et al 2012a |
| 13 | Visceral Leishmaniasis | Mice | $10^7$ cells/ mL | Single dose | Intravenous | Adhikari et al 2012b |

in humans – healthy or various diseases where it has been tried. Mayosi et al (2014) reported higher incidence of cancers in those treated with Prednisolone and MIP, however, no other studies have observed such associations.

**Dose and frequency of MIP vaccines:**

As discussed in preceding paragraphs and sections of this review, MIP/Mw has been extensively tried for different disease conditions. Table 1 summarizes various indications, dose of MIP, frequency and mode of administration for various disease conditions.

## Conclusion

While due to constraints of size and focus this review has not been able to include all the studies carried out on MIP, it is apparent that several studies have highlighted the usefulness of MIP as a broad spectrum immunomodulator, almost as a jack of all trades. It promises great hope in the future of medicine. Factors such as cost of production and safety profile should be considered carefully. If it turns out to be ideal MIP will be a savior especially in a country like India where both infectious diseases as well as cancers are significant health problems. Quicker recovery time in conditions like Covid-19 infection would be beneficial both financially and mentally. RCTs should be done to establish the role of MIP in HIV-infected individuals. Another question to be answered will be about the benefit of blanket immunization with MIP to reduce the incidence of various cancers, tuberculosis, and Covid-19 in the long term.

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