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Repurposing Metformin: An Update On Mechanism And Exploring Therapeutic Horizons

Pooja Raoa, Vikas Chauhanb, Shri Krishanc, Menka Singha, Radhikaa, Ritu Mishraa[a*]

[a]*Department of Pharmacy Practice, SGT College of Pharmacy, SGT University, Gurugram, Haryana, India.*
[b]*Department of Pharmaceutics, IIMT College of Pharmacy, Graeter Noida, Uttar Pradesh, India.*
[c]*Department of Drug Safety and Pharmacovigilance, Syneos Health, Gurugram, Haryana, India.*
[a*]*Department of Pharmacy Practice, SGT College of Pharmacy, SGT University, Gurugram, Haryana, India.*
*Corresponding Author: Dr. Ritu Mishra
*E-mail: ritu66mishra@gmail.com

Abstract
Metformin, a mostly prescribed drug for managing type II diabetes mellitus, has gained attention for its potential therapeutic benefits beyond glycaemic control. This review explores the multifaceted role of metformin as a potential adjuvant in various medical conditions, focusing on its antituberculosis activity, its impact on polycystic ovary syndrome (PCOS), and its anticancer properties. In the context of tuberculosis (TB), metformin has shown promise as an adjunctive treatment. Clinical studies have provided evidence of improved treatment outcomes in TB patients when metformin is added to conventional antituberculosis regimens. Furthermore, metformin enhances the host's immune response, potentially aiding in controlling latent TB infections. However, these findings are predominantly based on retrospective studies, highlighting the need for well-designed prospective clinical trials to establish metformin's role in TB therapy. Metformin's influence on PCOS, a common disorder affecting women of reproductive age, is another area of interest. Studies suggest that metformin can improve insulin sensitivity, regulate menstrual cycles, and reduce hyperandrogenism in PCOS patients. Its potential role in enhancing fertility and metabolic outcomes makes metformin a valuable option for PCOS management. Additionally, metformin has attracted attention for its anticancer properties. Preclinical and epidemiological data have indicated potential benefits in reducing cancer risk and improving outcomes in various malignancies. Metformin's ability to modulate key cellular pathways, such as AMP-activated protein kinase (AMPK) and mTOR, contributes to its anticancer effects. Metformin's versatile pharmacological profile extends its potential utility in diverse medical conditions, including tuberculosis, PCOS, and cancer. Continued research and prospective clinical assessments are essential to elucidate its precise mechanisms of action and to establish metformin's place as a valuable adjunctive therapy in these disorders.

Keywords: *Metformin, AMP-activated protein kinase (AMPK) and mTOR, diabetes mellitus, Anticancer, Antituberculosis, PCOD.*

1.INTRODUCTION

Metformin's glucose and insulin lowering capacity, as well as reduced glycogen synthesis, have been demonstrated to reduce blood sugar levels and benefit various conditions, including polycystic ovarian syndrome and metabolic disease. Numerous epidemiologic studies have connected metformin usage to a lower incidence of several cancers.[1] Metformin has several properties that make it suitable for use as an anti-cancer medication. It has been used for over 50 years and is most often recommended anti-diabetic drug worldwide.[2] It has been used in combination with most of cancer therapies without causing any significant interactions. Furthermore, data on metformin's toxicity profile in people without t2dm are are already accessible as a result of clinical research investigating its potential application as a polycystic ovarian syndrome treatment. Already available through clinical trials looking at its use as a therapy for polycystic ovary syndrome.[3] Patients with rectal and pancreas cancers who received metformin experienced a 30% increase in lifespan when compared to patients who received other anti-diabetic medications. Many studies have revealed that diabetic people who are treated with metformin have a decreased incidence and death from cancer.[4] The idea that biguanides are anticarcinogenic is not new. Previous research with phenformin, a biguanide temporarily utilized in people due to its higher tendency to generate lactic acidosis, revealed that it resulted in improved tumor cell growth reduction.[5] Polycystic Ovary Disease is a complex condition. Although it is primarily defined by high levels of testosterone, ovarian instability,

and polycystic ovarian geometry, its description is relatively flexible and contentious. The current study aimed to evaluate existing evidence-based and possible future applications of metformin in patients with PCOS. We focused on the impact of metformin medication on all characteristics and short-term or long-term PCOS problems. Metformin will also be examined as a preventive therapy in females at high risk of PCOS.[6] It is well known that chronic epithelial estrogen receptor deficiency caused by clomiphene's anti-estrogenic actions induces considerable endometrial shrinkage and, as a result, increases reproductive failure. Cervical mucus depression and endometrial thinning have been reported in 15% and 20-50% of Clomiphene citrate (CC) treatments, respectively, as compared to normal cycles.[7]

Five to ten percent of all women are thought to be impacted. PCOS is characterized by a number of signs, symptoms, and endocrine abnormalities. The effectiveness of clomiphene citrate (CC), the usual first-line medication used to induce ovulation in anovulatory women, varies; in general, women with PCOS and insulin resistance had the lowest success rate with CC. Insulin sensitizers have been shown to decrease hyperandrogenism and impaired insulin, and they are particularly useful in PCOS patients for promoting ovulation.[9] Tuberculosis (TB), caused by Mycobacterium tuberculosis, continues to kill approximately 1.43 million people annually worldwide. Although the current TB therapies are effective, they are time-consuming (6 to 9 month) and may cause side effects. Furthermore, as more and more TB germs develop medication resistance, new treatments are required. Metformin, a common medicine for diabetes, is being studied as a potential treatment for TB [10].

Numerous areas of research, including the avoidance of type II diabetes, have been interested in metformin due to its varied pharmacodynamic effects. Since type II diabetes is associated with a significant risk of vascular and macrovascular difficulties, as well as an increased risk of cardiovascular disease in those who already have the condition, efforts have been made to prevent type 2 diabetes in high-risk populations in order to reduce the possibility of long-term complications [11]. In multiple trials, diabetic individuals who received metformin have been less likely to develop infections, indicating that metformin may have antibacterial properties. In a new study, metformin was found to have a possible synergistic impact when taken with tetracycline against a high-resistance E. coli species in experimental animals. [12] Because of its non-antidiabetic benefits, including as a reduction in cardiovascular events, and its rather manageable side-effect profile, it is the first-line treatment for the majority of people with type 2 diabetes. [13]

Body cells have distinct tasks, and cell death is a normal occurrence known as apoptosis. A normal cell receives death orders, but malignant cells disregard these messages & continue to multiply and divide. [14] Cancer is defined by eight phenotypical traits that are involved in the disturbed regulation of cell functioning. They include persistent proliferative signaling, resistance to apoptosis, infinite replicative potential, evading immunological clearance, liberalizing cellular energetics, promoting angiogenesis, tissue invasion, and metastasis development. [15] Several studies in recent years have explored the mechanisms by which metformin may inhibit the growth of cancer cells [15].

One of the key ways metformin fights cancers is by affecting a pathway called AMP-activated protein kinase (AMPK). AMPK is an enzyme that senses energy levels in cells and helps control processes like glucose use and fat metabolism [16]. Metformin activates AMPK, which then blocks another pathway that is mammalian target of rapamycin (mTOR). This mTOR pathway is also crucial for controlling cell metabolism and growth [17].

The mTOR pathway is frequently overexpressed in cancer cells and is essential for encouraging cell division and development. Metformin may be able to decrease the growth and multiplication of cancer cells by blocking this route. It may also help make the cells more sensitive to chemotherapy or other cancer treatments. [18] Metformin is a common diabetes medication that may have potential as a cancer therapy, even if the precise processes by which it works as an anticancer agent are still being investigated. It's crucial to remember that additional study is required before insulin can be suggested as a routine cancer treatment, so patients should always speak with their doctors before beginning or discontinuing any medicine [19].

This review article encompasses a wide range of topics, including the potential role of metformin as an adjuvant in various medical applications such as tuberculosis, cancer, and polycystic ovary syndrome (PCOS). It also delves into future perspectives, exploring clinical insights and discussing the prospect of conducting prospective clinical assessments of metformin as an adjunctive treatment [19].

2.METFORMIN DRUG FOR ANTICANCER

Metformin, a commonly used medication for managing diabetes, has gained attention for its potential usefulness in cancer treatment and prevention. While it is not a primary cancer treatment, several mechanisms suggest how metformin might be beneficial in the context of cancer:

- AMPK, an enzyme that is essential for controlling the metabolism of cellular energy. Because AMPK activation throws off the energy balance of cancer cells, it can prevent them from growing and proliferating. This may result in less cell division, which would eventually halt the growth of the tumour [20,21].
- Insulin Sensitivity: Metformin improves insulin sensitivity in the body and reduces insulin levels. High insulin levels are associated to increased risk of certain cancers, including breast, colorectal, and prostate cancer. By lowering insulin levels, metformin may help reduce the risk of these cancers and potentially improve outcomes in individuals with insulin resistance or type 2 diabetes. [22]
- Reduction of Inflammation: Chronic inflammation is a hallmark of cancer progression and development of cancer. Metformin have an anti-inflammatory effect, which help in suppression of the inflammatory microenvironment within tumors. This can potentially slow down cancer growth and make tumors more responsive to treatment. [23]
- Decreased Cancer Cell Proliferation: Metformin can inhibit proliferation of cancer cells by interfering with various signaling pathways involved in cell growth. It may also induce programmed cell death in cancer cells. [24]
- Cancer Prevention: Some studies have suggested that metformin may reduce the risk of developing certain cancers, particularly in individuals with type II diabetes who are more likely to develop cancer. In certain situations, it might serve as a preventative strategy. [25]
- Tumor Microenvironment Modification: Metformin can alter the tumor microenvironment, making it less conducive to cancer cell survival and growth. It may reduce the availability of nutrients and oxygen to the tumor, making it more vulnerable to treatment. [26]
- Synergy with Standard Treatments: Metformin is often used in combination with standard cancer treatments like radiation therapy and chemotherapy. It might increase these medicines' efficacy by sensitizing cancer cells to their effects. Additionally, metformin might help mitigate some of the side effects associated with cancer treatments. [27]

It is crucial to remember that, even while metformin shows promise in the treatment and prevention of cancer, its efficacy can differ based on the kind and stage of the disease as well as unique patient characteristics. Usually, oncologists and other healthcare professionals create and oversee a comprehensive cancer treatment plan that includes metformin. Metformin's best use in various cancer scenarios is being determined by clinical trials and ongoing research, which is also advancing the exploration of its possible advantages in cancer care [28].

3. EXPLORING METFORMIN AS A HOST-DIRECTED THERAPY FOR TUBERCULOSIS: A NOVEL APPROACH TO TUBERCULOSIS TREATMENT

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (Mtb) and remains a major global health issue. TB is especially severe when combined with conditions like diabetes and HIV, and the rise of drug-resistant TB compounds the problem. In 2017, approximately 10 million people worldwide had TB, and 9% of them also had HIV. About 558,000 people had TB that was resistant to rifampicin, with 82% of these cases being multidrug-resistant (MDR) TB. Treatment success rates are around 80-85% for regular TB and 55-60% for MDR-TB. Standard TB treatment lasts 6 months, but treating drug-resistant TB takes longer [30,31].

4. EXPLORING THE RATIONALE BEHIND HOST-DIRECTED THERAPY FOR TUBERCULOSIS

"The intriguing relationship between microbes and the human host in the context of tuberculosis has persisted for a remarkably long time, as evidenced by historical records, resulting in significant morbidity and mortality. Mycobacterium tuberculosis (Mtb), the causative agent, demonstrates remarkable adaptability and successful interaction with the human host, as demonstrated by its ability to establish latent infections in approximately 23% of the global population [33]. This high infection rate can be attributed to the ability of certain Mtb strains to evade the host's immune responses, including both innate and adaptive defenses. These bacilli can persist in a state of dormancy when confronted with various stressors, such as changes in redox potential, pH fluctuations, and exposure to antimicrobial treatments."

Therefore, there is a compelling need to channel substantial resources and attention toward the advancement of supplementary immunotherapy, or more broadly, host-directed therapy, as an essential addition to our strategies for combating tuberculosis [34,35]. In recent years, there has been a surge in the discovery of potential candidates for host-directed therapy against TB, including several drugs and agents that have already demonstrated their effectiveness in managing various medical conditions like cardiovascular diseases, joint disorders, diabetes, and asthma [36,37].

5. METFORMIN'S HOST-DIRECTED THERAPEUTIC MECHANISMS IN TB

Recent laboratory research has increasingly highlighted the potential use of metformin (MET) in treating tuberculosis (TB) by targeting the host's own mechanisms. The following section will summarize these findings in a straightforward and scientific manner.

5.1. Macrophage activity

Previous studies have shown that metformin (MET) effectively stops the growth of Mycobacterium bovis, the H37Rv strain, and even multiple-drug-resistant strains of Mycobacterium tuberculosis (MDR strains) inside cells. This groundbreaking research aims to understand how MET works as a host-directed therapy for tuberculosis. It was found that MET's ability to inhibit bacterial growth depends on adenosine monophosphate-activated protein kinase (AMPK) signalling.

Further research revealed that MET increases the production of reactive oxygen species (ROS) from mitochondria, likely due to its interaction with the host cell's mitochondrial complex-1. This increase in ROS counteracts the mycobacteria's suppression of ROS production. The higher ROS levels may lead to cell apoptosis and death. Importantly, adding ROS-scavenging substances like glutathione and N-acetylcysteine stopped MET from inducing ROS, allowing the mycobacteria to grow inside cells again [39].

5.2. Autophagy

In the significant research that was previously mentioned, using MET not only encouraged the union of phagosomes with lysosomes within cells, but it also induced autophagy. It's interesting to note that preventing this autophagic activity did not appear to undo the MET's growth-inhibiting effects. More research is required to fully understand the potential roles of autophagy in containing or fighting Mycobacterium tuberculosis, regulating inflammation, and enhancing the host's innate and adaptive immune responses [40, 41]. This is especially important in light of the potential efficacy of MET in host-directed tuberculosis therapy.
Remarkably, recent research has demonstrated that MET can protect against spinal cord damage and cardiotoxicity caused by doxorubicin via regulating autophagy [42, 43].

5.3. Cell-mediated immune response

In the debate over whether the formation of granulomas in tuberculosis (TB) is helpful or harmful, researchers are exploring therapies that target these structures in the body's response to the disease. The aim is to either boost the body's natural defenses and healing mechanisms or to reduce the damage caused by advanced granuloma formation.[44] One such therapy being investigated is MET, which has shown promising results in reducing tissue damage and improving the immune response in TB. When tested in mice, MET treatment led to less lung damage and fewer granulomas, along with increased infiltration of lymphocytes (a type of white blood cell important for immunity). Additionally, MET-treated mice tended to have higher numbers of CD4+ and CD8+ T cells, which are involved in fighting off infections like TB. It would be helpful to further study the specific types of T cells involved, such as Th1, Th2, and T regulatory cells. [45,46]

Many studies have found that MET reduces the activity of genes linked to inflammation, such as interleukin-1 beta, tumour necrosis factor-alpha, interleukin-6, monocyte chemoattractant protein-1, and intercellular adhesion molecule-1. This effect is likely due to its impact on AMPK and nuclear factor kappa-B pathways. In mouse experiments, MET also helped lessen lung fibrosis through a mechanism involving AMPK [47,48]

5.4. Oxidative Stress

In recent years, many studies have looked into how metformin (MET) affects oxidative stress, which is a key factor in diseases like type 2 diabetes mellitus (T2DM) and tuberculosis (TB), especially in diabetic patients. [49]
One study with male mice found that long-term MET use improved their health span and life span. [50] At a molecular level, MET boosted the activity of a protein called AMPK, which helps protect against oxidative stress and reduces chronic inflammation. Another study in diabetic rats showed that MET helped control oxidative stress by affecting the activity of enzymes like catalase and superoxide dismutase in their muscles. Similarly, in rats with gum disease (periodontitis), MET reduced inflammation and bone loss. [51,52]
While one study observed an increase in reactive oxygen species (ROS) in certain cells exposed to MET, another study in human cells found that MET stimulated AMPK activity, reduced ROS production, and increased the expression of certain antioxidant genes. [53]
Clinical trials in diabetic patients showed that MET improved their antioxidant levels and reduced inflammation. Compared to lifestyle changes alone, MET also showed better outcomes in terms of oxidative stress and antioxidant levels in diabetic patients. [54,55]
Recent research suggests that MET might protect against oxidative stress-related complications in diseases like diabetes. [56] This could be particularly relevant in TB, where diabetic patients often have worse outcomes due to oxidative stress weakening their immune response. [57]
Understanding how MET reduces oxidative stress could be important for its role as a host-directed therapy in TB. [58] Although more research is needed, it's possible that MET's anti-inflammatory and antioxidant properties work together through different cellular pathways. [59,60]
If MET's ability to reduce oxidative stress proves to be a key mechanism in TB treatment, it could have significant implications for other diseases like diabetes and HIV, which also involve oxidative stress in their progression. [61]

5.5. Anti-microbial activity

A fascinating finding came from a computer-based analysis, showing a possible different way Mycobacterium tuberculosis (Mtb) persisters generate energy. This process involves changing how certain molecules flow through specific pathways, namely the NAD biosynthesis pathway and a part of the respiratory system called complex-1 (NDH-1). [62]. There are similarities between a part of the respiratory system in bacteria called NDH-1 and a similar system found in mitochondria, called complex-1. This similarity suggests that metformin (MET) might not only affect the complex-1 in human cells but also the NDH-1 in Mycobacterium tuberculosis (Mtb), the bacteria causing tuberculosis. If MET does indeed impact NDH-1 in Mtb, it could potentially fight the bacteria directly. However, not much research has been done in this area yet, so more exploration is needed to confirm this possibility. [63] In a follow-up study by the original researchers, they found that using metformin (MET) alongside standard tuberculosis medications had positive effects in animal experiments. Specifically, MET made isoniazid and ethionamide, two important TB drugs, work better in both short-term and long-term TB models in mice. However, it's important to mention that not all animal studies have definitively shown that MET improves tuberculosis treatment when used alongside standard drugs. [64].

6. EXPLORING THE SYNERGISTIC EFFECTS OF ANTITUBERCULOSIS DRUGS AND METFORMIN IN MURINE EXPERIMENTS

In a recent study involving mice with TB, researchers added metformin (MET) to the standard TB drugs but noticed only a slight improvement in killing the TB bacteria, which wasn't big enough to be considered significant. Additionally, there was no sign that MET made the standard drugs more effective at completely getting rid of the TB bacteria, as seen in the relapse rates after different treatment periods. [65,66]
There are several reasons why the recent study's results might differ from the original one. Firstly, they may have used different types of mice for their experiments. [67] Additionally, the way the experiments were set up was different: the earlier study tested metformin (MET) alone, while the recent one looked at how MET works alongside standard TB drugs. [68,69]
Additionally, including rifampicin in the recent study might have affected how MET is processed in the body. One important factor to consider is the organic cation transporters that help move MET around, although there

could be other enzymes and transporters involved as well. [70]. Recent studies have shown that moxifloxacin can strongly interfere with how metformin (MET) and ethambutol are processed in the body in laboratory settings. Drug interference occurs through organic cation transporters and multidrug and toxin extrusion proteins. These drug interactions are crucial to consider for future animal experiments [71].

7. CLINICAL INSIGHTS INTO TUBERCULOSIS OUTCOMES WHEN METFORMIN IS USED AS AN ADJUNCTIVE TREATMENT

Clinical data on tuberculosis (TB) outcomes about metformin (MET) usage are summarized as follows.

7.1. Latent infection due to MTB

In clinical part of the previous studies, researchers looked at the results of a test called T-SPOT.TB in diabetic patients. This test measures the immune response to latent tuberculosis (TB) infection by detecting interferon-gamma release. They found that metformin (MET) treatment might improve the body's immune response against latent TB infection, with a protective effect suggested by the odds ratio of 0.44 (95% confidence interval: 0.20 to 0.95). In a separate study conducted in India, researchers compared 152 diabetic patients who had tuberculosis (TB) with 299 diabetic patients who did not have TB. This was done through a retrospective case-control study [72]. Among people with tuberculosis (TB), only 25.5% were taking metformin (MET), while 57.1% of those without TB (the control group) were using MET. MET was found to reduce the risk of developing TB in individuals with diabetes, with an odds ratio of 0.256 (95% confidence interval: 0.16 to 0.40). Another study in East Asia examined a large group of diabetic patients and found that those who took MET for at least 60 days and used sulfonylureas for less than 15 days (called "MET majors") had a much lower risk of developing active TB. The adjusted hazard ratio was 0.477 (95% confidence interval: 0.268 to 0.850), indicating that the protective effect of MET increased with higher doses. This protective effect was observed regardless of the patients' blood sugar control, and the study took into account other factors like statin use [73].

In a different study conducted in the same area, the use of metformin (MET) was linked to a lower risk of developing active tuberculosis (TB) even after considering other factors. The adjusted relative risk was 0.24 (95% confidence interval: 0.18 to 0.32), which is consistent with the findings of the previous large study [74].

7.2. TB disease

Although it was not statistically significant, it was noted in the clinical portion of the first trial that diabetics with diabetes had type 2 diabetes who did not use metformin (MET) appeared to have an increased risk of advanced pulmonary disease on X-ray examination. A statistically significant distinction in lung cavities was observed between diabetic patients who used MET and those who did not. Additionally, multivariate analysis revealed that MET-using diabetic TB patients had a lower death rate [75].

105 people with diabetes with tuberculosis were examined in retrospective research conducted in South Korea; 62 of them were on MET, and 43 are not., the groups were similar in terms of initial characteristics. MET use did not significantly affect how quickly TB bacteria disappeared from sputum after two months of treatment or the likelihood of TB coming back within a year after treatment. However, among diabetic patients with lung cavities, those taking MET were significantly more likely to have the TB bacteria disappear from their sputum after two months of treatment [76] In another study looking at 2,416 patients with tuberculosis (TB), those who also had diabetes mellitus had a higher risk of dying during TB treatment and were more likely to still have TB bacteria in their system after two months of therapy compared to patients without diabetes. Surprisingly, even though some diabetic patients had similar or worse blood sugar control, those who were taking metformin (MET) had a significantly lower risk of dying during their TB treatment. [77].

In a review of 58 patients in China with both type 2 diabetes and culture-positive pulmonary tuberculosis (TB), only 27.6% were taking metformin (MET). Despite no significant difference in blood sugar control between those taking MET and those not, patients on MET had higher rates of successful TB treatment and sputum culture conversion after two months compared to those not taking MET. Specifically, 93.8% of MET users had successful treatment compared to 71.4% of non-users, and 87.5% of MET users had sputum culture conversion compared to 71.4% of non-users. Additionally, over a three-year follow-up period after treatment, TB relapse rates were significantly lower in the MET group (6.3%) compared to the non-MET group (35.7%) [78,79].

7.3 Prospective Clinical Assessments of Metformin as an Adjunctive Treatment in Tuberculosis

Many clinical studies from various parts of the world have shown positive results in treating tuberculosis (TB) when metformin (MET) is used alongside standard TB medications. However, it's important to note that all these studies published so far have been looking back at past data, which is called retrospective. To truly confirm whether MET helps in TB treatment, including cases resistant to drugs, we need studies where patients are randomly assigned to different treatments and closely monitored over time. These studies, called prospective randomized controlled clinical trials, are necessary. Additionally, well-designed studies that follow groups of patients over time, called prospective cohort studies, could also provide valuable insights into the benefits of using MET in TB treatment. [80].Besides confirming whether metformin (MET) effectively helps the body fight different forms of tuberculosis (TB), these trials should also look into how MET interacts with other drugs, as mentioned earlier. They should also check for any negative effects or harmful reactions caused by MET alone or when it interacts with other TB drugs, both the traditional ones and any new ones being tested [81]. MET can cause mild side effects like upset stomach, but also rare but serious issues like lactic acidosis [81,82]. When planning these studies, it's crucial to carefully choose the dose of metformin (MET) being tested. This is important because MET can affect metabolism, cause toxicity, and influence how the immune system works. It's also necessary to take into account the patient's heart, kidney, and liver functions when deciding on the right dose for the clinical trials [83,84]. By considering these factors, researchers can determine the best and safest dose(s) of MET to use in the studies, ensuring that the potential benefits outweigh any risks associated with the medication. This approach will help maximize the effectiveness of MET as a treatment for tuberculosis (TB) while minimizing any potential harm to patients [85]

S. No	Outcomes	References
1	Preventing latent infections from becoming active diseases.	86, 87, 88
2	Reduced formation of lung cavities.	89
3	More sputum samples testing negative for TB bacteria after two months of treatment.	90
4	Reduced death and recurrence of the disease in patients.	91, 92

Table 1: Results of reported TB treated with metformin as an adjuvant.

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