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Screening of Pharmaceutically Significant Methioninase-Producing Fungi from the Satpura Range of Hoshangabad District and Its Large-Scale Production

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Abstract

L-methioninase, an enzyme with notable anticancer properties, has emerged as a promising therapeutic agent due to its ability to selectively degrade methionine, a critical amino acid for the survival of methionine-dependent cancer cells. Methionine dependency, observed in many tumor cells, is a metabolic vulnerability that can be exploited for targeted cancer therapy. The Satpura Range in the Narmadapuram District, India, with its diverse microbial ecosystems, offers a rich reservoir for the discovery of methioninase-producing fungi. This study aimed to systematically explore the fungal biodiversity of this region to identify potent methioninase producers, optimize enzyme production, and evaluate their potential for large-scale synthesis. Soil and organic matter samples were collected from four distinct ecological locations, and fungal isolates were screened for methioninase activity using selective culture media containing methionine as the sole carbon source. Promising isolates were subjected to morphological, microscopic, and molecular identification to ensure accurate taxonomy. Key production parameters, including temperature, pH, carbon and nitrogen sources, and trace elements, were optimized to enhance enzyme yield. Large-scale production was achieved through liquid-state fermentation, yielding significant quantities of methioninase with high purity as confirmed by SDS-PAGE analysis. The findings underscore the untapped potential of Satpura's microbial diversity in pharmaceutical enzyme research and establish a foundation for the cost-effective and sustainable production of methioninase for therapeutic applications. This study paves the way for future research into the clinical efficacy of methioninase-based cancer therapies, contributing to advancements in enzyme biotechnology and cancer treatment.

Keywords: Methioninase, indigenous fungal isolates, liquid-state fermentation, cancer therapy, personalized medicine, enzyme characterization

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INTRODUCTION

Enzymes are exceptional biocatalysts essential for facilitating biochemical reactions in living organisms, enabling them to function under mild conditions of temperature, pH, and pressure. These large biomolecules are central to sustaining life by catalyzing a wide array of chemical conversions in metabolic pathways [1–5]. Their remarkable catalytic efficiency accelerates reactions by factors ranging from 100 million to 10 billion times compared to traditional chemical reactions, enabling organisms to thrive in diverse environments. Beyond biological systems, enzymes have diverse industrial applications, such as in the production of sweetening agents, antibiotic modification, cleaning products, and diagnostic assays in clinical and environmental contexts. Their

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use in industrial processes is aligned with green chemistry principles, as they catalyze reactions under mild conditions, reducing the need for harsh chemicals, extreme temperatures, and minimizing toxic by-products, thus promoting sustainability [6–13].

Microorganisms, including bacteria, fungi, and actinomycetes, are valuable sources of bioactive compounds, including enzymes. These organisms produce a wide range of metabolites that serve defensive, protective, and symbiotic purposes, with bacteria and fungi emerging as particularly effective enzyme producers. Microbial enzymes, especially those from extremophiles, are prized for their stability and activity under harsh conditions, such as high temperature and fluctuating ph. Genetic engineering techniques allow for the optimization and overexpression of enzymes, enhancing yields and tailoring enzyme properties for specific applications [14–19]. The pharmaceutical industry, in particular, benefits from microbial enzymes, which are used in drug production and directly as therapeutic agents, such as in enzyme replacement therapies and cancer treatments [20–25].

L-methioninase, an enzyme with significant therapeutic potential, is a promising anticancer agent. L-methioninase catalyzes the degradation of methionine, an essential amino acid for cellular processes, producing α-ketobutyrate, methanethiol, and ammonia. This enzyme selectively targets cancer cells that are methionine-dependent, depriving them of this vital nutrient and inhibiting their growth. L-methioninase has shown efficacy against a range of tumor cell lines, including those of breast, lung, colon, kidney, and glioblastoma. The enzyme is produced by various microorganisms, including bacteria, fungi, and marine microbes, and has been extensively studied for its role in cancer therapy. Its selective action on methioninedependent cancer cells makes it an attractive candidate for targeted cancer treatments with minimal impact on healthy tissues [26–32].

Microbial sources, particularly bacteria and fungi, are the primary focus for large-scale Lmethioninase production due to their ability to be cultured efficiently. Species, such as Pseudomonas and Aspergillus have been explored for their high enzyme yields. Fungal Lmethioninase offers advantages over bacterial sources, such as reduced immunogenicity, making it a promising alternative for therapeutic applications. Recent studies have also investigated plant sources of L-methioninase, including Arabidopsis thaliana, with potential agricultural and biotechnological applications [33–39].

AIM OF PROPOSED STUDY

The Narmadapuram District, located in central India, offers a unique ecological setting with diverse biogeographical features that foster rich microbial biodiversity. This study aims to explore the potential of Indigenous fungi in the region to produce L-methioninase, particularly from locations, such as Hirapur, Jirran, Paraswada, and Patharai villages. The focus is on discovering novel fungal species capable of producing L-methioninase for industrial and therapeutic applications [40–48].

This research seeks to bridge the gap between microbial biodiversity and its practical applications in biotechnology and pharmaceuticals.

MATERIALS AND METHODS

Sample Collection

Soil and organic matter samples were collected from Hirapur, Jirran, Paraswada, and Patharai villages within Sohagpur Tehsil of the Hoshangabad District. Sampling sites included forest floors, decaying organic matter, and agricultural zones. Sterile tools and aseptic techniques were employed to ensure the integrity of the samples, which were transported to the laboratory in sterile, airtight containers. A random sampling method was employed, with detailed sampling locations listed in Table 1.

PRELIMINARY ISOLATION AND PURE CULTURE PREPARATION

Media Preparation

To isolate and screen fungi from the collected soil samples, Potato Dextrose Agar (PDA) and Sabouraud Dextrose Agar (SDA) media were chosen due to their effectiveness in promoting fungal

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growth while preventing bacterial contamination. These media were sourced from HiMedia Laboratories Pvt. Ltd., known for high-quality microbiological media. The compositions of PDA and SDA are provided in Tables 2 and 3, respectively.

Table 1. Sampling Locations and Descriptions of Soil and Organic Matter Samples Collected from Sohagpur Tehsil.

S.N.	Sampling Points	Sample Description	Sample Code
1	Hirapur	Black soil, granulated form	A1
2	Jirran	Black soil, granulated form	A2
3	Paraswada	Black soil, granulated form	A3
4	Patharai	Black soil, powder form	A4

Table 2. Composition of Potato Dextrose Agar (PDA) Medium Used for Fungal Isolation.

S.N.	Ingredients	Quantity in Grams/Liter
1.	Potatoes, infusion from	200 gm
2.	Dextrose	20 gm
3.	Agar	15 gm
4.	Final pH	5.6 ± 0.2

- *Potato Dextrose Agar (PDA):* A nutrient-rich medium derived from potato infusion and dextrose, adjusted to a pH of 5.6 ± 0.2 for fungal growth.
- *Sabouraud Dextrose Agar (SDA):* Contains a higher concentration of dextrose and mycological peptone, also with a pH of 5.6 ± 0.2, ideal for growing pathogenic and saprophytic fungi.

Table 3. Composition of Sabouraud Dextrose Agar (SDA) Medium Used for Fungal Isolation.

S.N.	Ingredients	Quantity in Grams/Liter
1	Dextrose	40 gm
2	Mycological Peptone	10 gm
3	Agar	15 gm
4	Final pH	5.6 ± 0.2

Both media were prepared according to the manufacturer's instructions, followed by autoclaving. Once cooled, the media were poured into sterile Petri dishes under aseptic conditions (Figure 1).

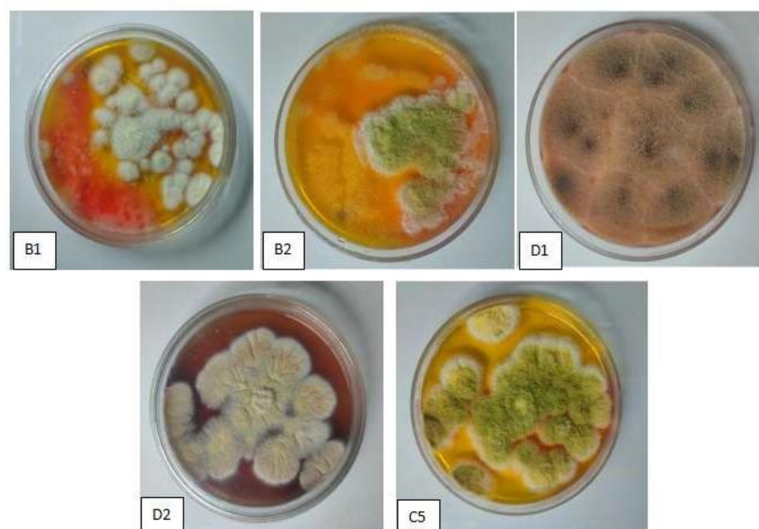

Figure 1. Methioninase-producing unknown Indigenous fungal isolates.

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FUNGAL ISOLATION

Soil fungi were isolated by serial dilution of the samples (dilutions of 10^{-5}, 10^{-7}, and 10^{-9}) and plating them onto PDA and SDA media using the spread plate method. After incubation at 27°C for 3 to 5 days, colonies with distinct morphology were selected for further study.

Fifteen primary culture plates were established, and the most representative colonies were selected based on phenol red color change and colony morphology. Pure cultures were obtained by sub-culturing on fresh PDA plates under the same conditions [49–54].

Screening for Methioninase-Producing Fungi

The screening aimed to identify fungal isolates capable of producing methioninase. Methioninase activity was detected by the release of ammonia in the culture medium, which caused an increase in pH, turning the phenol red from yellow to red.

Fungal isolates were cultured on PDA plates with methionine and phenol red. This method allowed for differentiation between methioninase-positive and negative isolates. Out of the 15 isolates tested, 5 were found to produce methioninase, as shown in Figure 1.

In Vitro Methioninase Production

The 5 methioninase-positive fungal isolates were selected for in vitro enzyme production via liquid-state fermentation. The fermentation medium was carefully prepared based on established protocols to ensure optimal fungal growth and enzyme production. Fermentation was conducted under controlled temperature and agitation conditions for a specific period.

Study on Media Optimization Parameters

To enhance methioninase production, optimization of fermentation conditions was carried out by varying carbohydrate sources, pH levels, and temperature. The fermentation process was conducted for five days, with the supernatants analyzed for ammonia content using Nessler's method, which is described in detail later.

The results indicated that carbohydrate type and pH had the most significant impact on enzyme production, while temperature had a more limited effect. Combining the optimal conditions for each parameter led to a significant increase in methioninase production, as shown in Table 4 [55–59].

Table 4. L-Methioninase Production by Different Fungal Isolates Under Optimized Fermentation Conditions.

S.N.	Fungal Isolate	Percentage L-Methioninase Produced
1	B1	30.76
2	B2	24.10
3	D1	30.34
4	D2	44.62
5	C5	42.22

Outcomes of Methioninase Production on Optimized Parameters

Optimized conditions led to improved enzyme yields. Fungal isolate D2 was the highest producer of methioninase, with a yield of 44.62%, followed by C5 with 42.22%. Other isolates, B1, D1, and B2, produced methioninase at 30.76%, 30.34%, and 24.1%, respectively as shown in Figure 2. Given the exceptional production from D2 and C5, these isolates were selected for further molecular identification via Sanger sequencing of the internal transcribed spacer (ITS) region of their genomes. This step will help confirm their species and provide insight into the genetic basis for their high methioninase production. This genomic analysis is crucial for potential biotechnological applications, as it could lead to the development of improved strains for industrial-scale enzyme production [60–65].

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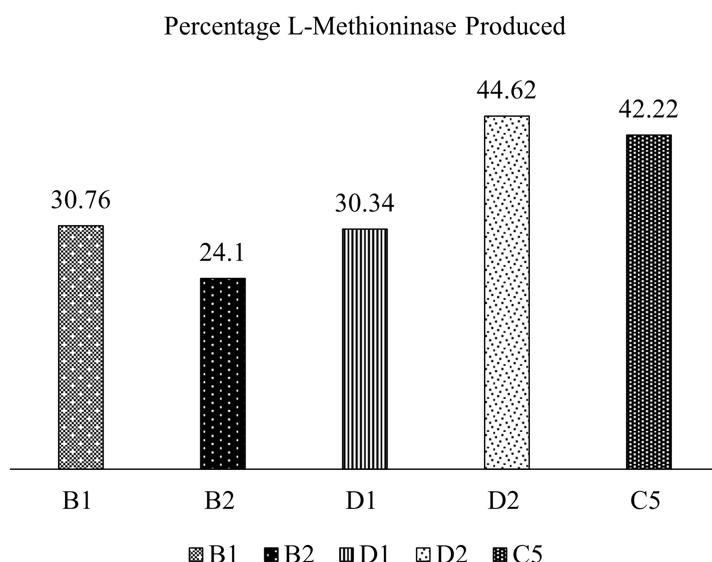

Figure 2. Graphical description of L-Methioninase produced by Indigenous fungal isolates at combined optimum LSF parameters.

Large-Scale Production

Liquid-state fermentation was employed to scale up methioninase production. Selected fungal isolates were cultivated in optimized liquid media under controlled conditions in a rotary shaker. Enzyme extraction involves mechanical disruption of fungal biomass followed by centrifugation to obtain the enzyme-rich supernatant. Methioninase activity was quantified using a spectrophotometric assay, measuring the production of α-ketobutyrate.

RESULTS AND DISCUSSION

The molecular characterization and identification of fungal species is a crucial process for understanding their genetic makeup and functional properties, particularly in relation to enzyme production. This process begins with the extraction of high-quality genomic DNA from fungal strains, which is essential for the accuracy of subsequent analyses. DNA extraction involves disrupting fungal cells through a lysis method, followed by the purification of the DNA to remove contaminating cellular components like proteins and lipids. The purified DNA serves as the template for amplifying the Internal Transcribed Spacer (ITS) region, a genetic marker frequently used in fungal identification due to its variability across species.

To amplify the ITS region, polymerase chain reaction (PCR) is employed, utilizing primers that target conserved sequences flanking the variable ITS region. PCR conditions are optimized to ensure efficient amplification specific to the fungal species under study. Following amplification, the ITS region is sequenced using high-throughput genome sequencers, which determine the nucleotide sequence of the region. The resulting sequences are then compared against a fungal database, typically using the Basic Local Alignment Search Tool (BLAST) from the National Center for Biotechnology Information (NCBI), to identify the closest species match based on sequence similarity (Table 5).

Table 5. The sequences of forward & reverse ITS primer pair.

Primer	Sequence
ITS1 (forward)	5-TCCGTAGGTGAACCTGCGG-3
ITS4 (reverse)	5-TCCTCCGCTTATTGATATGC-3

In this study, the fungal isolates that demonstrated high methioninase production were subjected to molecular characterization using the aforementioned steps. Specific adjustments were made to the DNA

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extraction and PCR protocols to optimize them for the isolates in question, ensuring the accuracy and reliability of the identification process. This molecular approach allowed for the precise identification of the fungal species, contributing to a better understanding of the genetic factors involved in their methioninase production capabilities.

Molecular characterization is essential for confirming the identity of fungal strains, as it helps determine whether the species is novel or known. Furthermore, this process can provide valuable insights into the genetic characteristics responsible for methioninase production, which has significant industrial and biotechnological implications. The results from sequencing and subsequent BLAST analysis were pivotal in identifying the species of the potent methioninase producers and will inform future research on their potential applications in enzyme production (Figure 3).

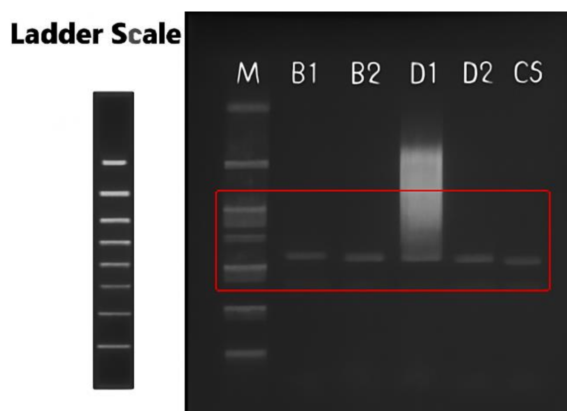

Figure 3. Amplified fragment by PCR run on 1% agarose gel indicating ITS region using primers ITS1/ITS4.

Additionally, a detailed protocol for genomic DNA extraction, PCR amplification, and sequencing was followed to ensure high-quality results, enabling accurate species identification and characterization of the methioninase-producing isolates used in this study.

SDS-PAGE Analysis of Fungal Methioninase

This study focused on the molecular characterization of methioninase produced by selected Indigenous fungal isolates. The fermentation extracts of fungal isolates B1, B2, D1, D2, and C5 were harvested after cultivation in optimized liquid-state fermentation (LSF) media. Protein concentrations in the extracts were measured using the Bradford method, with values ranging from approximately 50 to 100 µg/ml, as detailed in Table 6. This protein quantification was crucial for loading an appropriate amount of protein for the SDS-PAGE analysis, ensuring the accurate visualization of methioninase enzyme bands.

Table 6. Absorbance of the standard sample (Bovine serum albumin) at 595 nm wavelength.

S.N.	Extracts Salted Out	OD at 595 nm	Concentration (µg/ml)
1	B1	2.036	61.93
2	B2	2.269	84.05
3	D1	1.842	61.85
4	D2	1.622	50.41
5	C5	2.159	68.33

Protein concentrations were determined by comparing optical density (OD) values to a calibration curve based on bovine serum albumin (BSA). The estimated protein content of these extracts was optimal for generating distinct bands during SDS-PAGE analysis.

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Gel Imaging and Banding Pattern of Fungal Methioninase

The crude enzyme extracts from the fungal isolates were subjected to SDS-PAGE for methioninase characterization. A standard L-methioninase enzyme (Sigma Aldrich, M2560) and a protein molecular weight marker (MBT092, HiMedia) were included for comparison. The enzyme extracts were labeled E1 to E5, representing B1, B2, D1, D2, and C5, respectively.

Using a 12% SDS-PAGE gel, the protein bands were well-resolved. Distinct bands appeared in the extracts of B1 and B2 (E1 and E2) at the same position as the standard L-methioninase, confirming the presence of the enzyme. Although fainter bands were observed in the extracts of D1, D2, and C5 (E3, E4, and E5), they still indicated the presence of methioninase at a similar position to the standard enzyme (Figure 4).

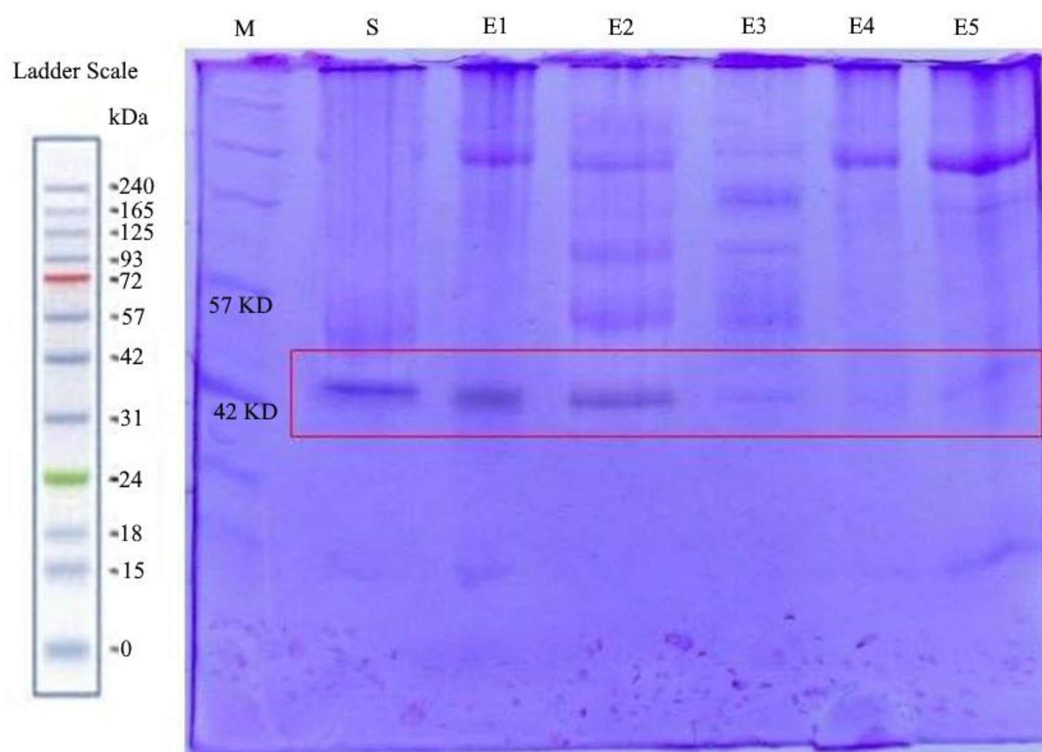

Figure 4. SDS-PAGE gel image and sharp banding pattern of protein of interest at the level of 42 KD marker range, indicative of the presence of L-methioninase present in a loaded sample.

The molecular weight of the L-methioninase enzyme in both the standard and fungal extracts aligned closely with the 42 KD marker range, as shown in the SDS-PAGE gel. This confirmed that the molecular weight of methioninase in the extracts was approximately 43 KD, consistent with published studies, where the enzyme's molecular weight typically ranges from 40 to 50 KD.

These findings validate the successful secretion of methioninase by the Indigenous fungal isolates under optimized fermentation conditions, contributing valuable insights into its molecular characteristics.

CONCLUSION AND FUTURE SCOPE

This research explored the production, characterization, and potential applications of methioninase derived from Indigenous fungal isolates. By optimizing conditions for liquidstate fermentation (LSF) and fungal growth, it was demonstrated that the selected strains (B1, B2, D1, D2, and C5) produced methioninase in significant quantities. The protein content of the fermentation extracts ranged from 50 to 100 µg/ml, and SDS-PAGE analysis confirmed the enzyme's presence with a molecular weight of

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approximately 43 KD, aligning with established data for methioninase. These findings establish a solid foundation for further exploration of methioninase in various therapeutic applications.

The research highlighted the potential of methioninase in cancer therapy, owing to its ability to selectively deplete methionine, an essential amino acid for tumor cell proliferation. Additionally, the enzyme's utility in managing metabolic disorders, drug development, and personalized medicine was underscored, demonstrating its broad therapeutic potential in addressing diseases associated with methionine metabolism. Methioninase's ability to complement conventional therapies, like chemotherapy and radiation, presents an exciting avenue for combination therapies, potentially enhancing treatment efficacy and minimizing side effects.

Looking ahead, several promising avenues for future research were identified. First, expanding the exploration of fungal biodiversity, particularly in ecologically rich regions, such as the Satpura Range, could lead to the discovery of new, more efficient methioninase-producing strains. The application of genetic engineering techniques could further optimize enzyme production and activity in selected fungal strains, facilitating large-scale production for both industrial and therapeutic purposes. Clinical trials and translational research are crucial next steps to assess the safety, efficacy, and appropriate dosing of methioninase-based therapies. In addition, investigating combination therapies and the pharmacokinetics and pharmacodynamics of methioninase will be essential for refining treatment strategies, particularly for cancer and metabolic disorders.

Furthermore, integrating bioinformatics and systems biology approaches will enhance the precision of methioninase-based therapies, enabling the tailoring of treatments to individual genetic and metabolic profiles. This personalized approach could revolutionize the effectiveness of therapies, improving patient outcomes, particularly for cancer and metabolic diseases.

In conclusion, this study provides a solid foundation for the application of methioninase in therapeutic settings, with the potential to transform cancer treatment, metabolic disorder management, and drug development. As research advances, methioninase could play a central role in personalized medicine, offering safer, more effective treatment options for patients worldwide.

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