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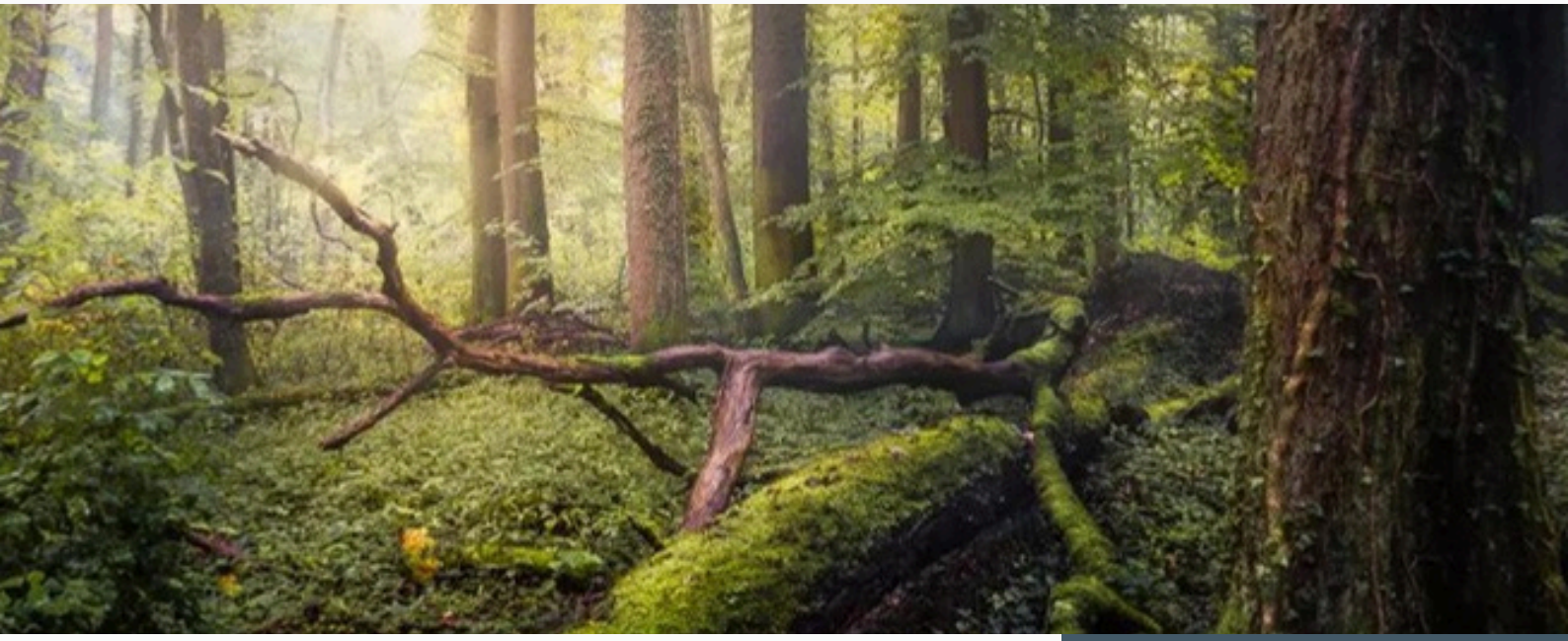

PSYCHROTOLERANT AND PSYCHROPHILIC FUNGI FERMENTATION: GREAT POTENTIAL FOR PHARMACEUTICAL EXPLORATION THROUGH NATURAL SOURCES

The Evolution of Fermentation Throughout History

Natural products account for 60% of the total market, making them a major source of drug discovery. Some of these are sourced from the cultivation of microorganisms. This approach started with Fleming's serendipitous discovery of penicillin from the filamentous fungus, Penicillium notatum in 1929. His findings have raised the intensive investigation of nature as a source of novel bioactive agents. The broad chemical diversity of natural products, in addition to their strong correlation to biological functionality, is the justification for the necessity to constantly nurture natural products in today's discovery efforts.

Fermentation is broadly defined as the biochemical changes in organic substances carried out by enzymes produced by microorganisms or other living cells. For thousands of years, traditional biological processes have been used. Early civilizations keenly observed the decay of trees, the decomposition of deceased organisms, and the spoilage of food, leading to the development of innovative methods for producing a diverse array of fermented products. This includes the age-old techniques employed in creating bread, wine, beer, vinegar, cheese, pickles, and other fermented products. The history of the use of fermentation for the fulfilment of human needs can be traced back to approximately 10,000 B.C., during a time the underlying mechanism of fermentation remained largely unknown. However, around 4,000 B.C., the ancient Egyptians made a significant breakthrough by discovering the role of carbon dioxide, which is generated by brewer's yeast, in bread leavening.

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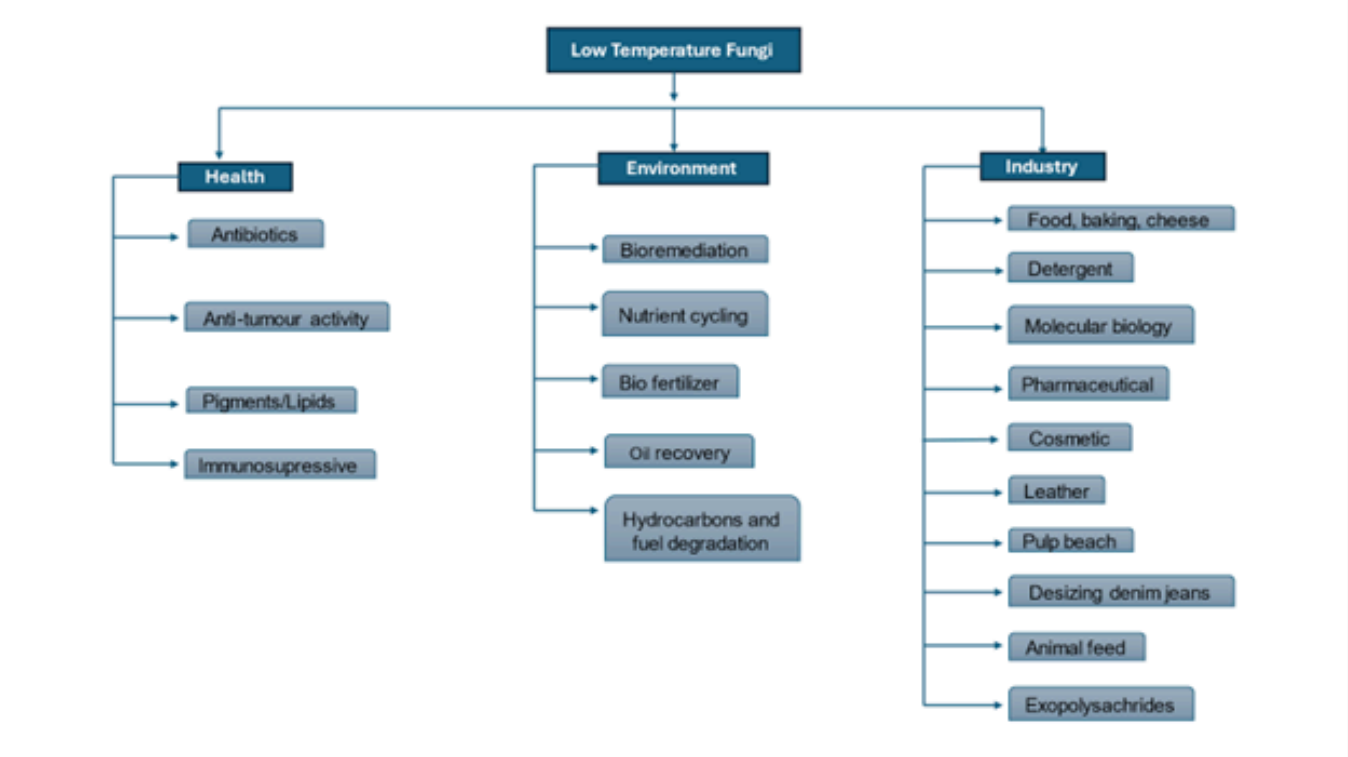
Prior to 3,000 B.C., individuals had already achieved the remarkable feat of fermenting juices into alcoholic beverages by realising the fact that fruits containing sugar spontaneously fermented during storage. Ancient Assyrian records dating back to before 2,000 B.C., provide evidence of wine production in that region. It was around 1150 B.C. that the process of distilling alcoholic beverages yielded ethanol for the first time. It is called the “spirit of wine”, as it is frequently obtained from wine. In 1676, Antoni van Leeuwenhoek was the first to observe microorganisms with his newly built microscope and, for the first time, visualised yeast cells. In 1857, Louis Pasteur first claimed that the production of beer and wine through fermentation was a result of microbial activity rather than a chemical process. He also pointed out that some fermentations are aerobic, and others are anaerobic. In subsequent years, significant advancements were made by a scientist named Hansen. He revolutionised beer making by developing and cultivating yeast.

In 1897, Buchner’s discovery marked a significant milestone as he discovered the ability of enzymes extracted from yeast to convert sugar into alcohol. In 2000, large-scale sewage treatment was carried out by employing microbes in Berlin, Hamburg, Paris, and other western cities. In 1913, a pivotal moment arrived with the first successful industrial-scale fermentation process, enabling the production of three vital chemicals—acetone, butanol, and glycerols—through bacterial fermentation.Alexinder Fleming's breakthrough in biotechnological research was the production of the antibiotic penicillin.. This key moment took place in the realm of fermentation, illustrating the far-reaching impact of microbial studies on medical advancements. It was in 1937, that Mamoli and Vercellone unveiled the field of microbial transformation by showcasing the conversion of dehydroepiandrosterone to testosterone by cynobacterium mediolanum and yeast. The 1940s saw the identification of numerous new antibiotics, paving the way for the large-scale production of penicillin. Later in the 1950s, the microbial conversion of steroids emerged as a major field for the biotechnological and pharmaceutical industries.

Psychrotolerant Fungi and Fermentations

The mass culture of fungi holds immense importance as they act as producers of diverse commodities that possess significant industrial value. These commodities include enzymes, such as cellulases and lipases. Additionally, fungi biomass, exemplified by Brewer's yeast, serves as an invaluable resource for numerous applications. Fungi also produce metabolites that have wide-ranging industrial implications, including antibiotics, statins, and vitamins. Furthermore, the production of recombinant products through fungal mass culture has revolutionised the biotechnology field. Examples of such products include insulin, interferon, and human serum albumin. Moreover, transformation processes in fungal mass culture generate metabolites that possess structural similarities to existing compounds. These metabolites offer immense potential for the development of new drugs, agrochemicals, and other high-value products.

A schematic representation of how metabolites of psychrotolerant and psychrophilic fungi are exploited in different fields is illustrated in Scheme 1 (Hassan et al., 2016).



SCHEME 1: SCHEMATIC REPRESENTATION OF HOW METABOLITES OF PSYCHROTOLERANT AND PSYCHROPHILIC FUNGI ARE EXPLOITED IN DIFFERENT FIELDS ACCORDING TO HASSAN ET AL. (2016)

Psychrotolerant organisms play a crucial role in various industrial processes that demand high enzymatic activity, particularly at low temperatures. This is primarily due to the presence of cold-adapted enzymes within these organisms, enabling them to function efficiently in cold environments. For instance, Mortierella minutissima is a novel psychrotolerant fungus that is used in the biotransformation of D-limonene (M. Trytek et al., 2015). Another noteworthy psychrotolerant fungus is Chrysosporium pannorum, which serves a vital role in the bioconversion of α-pinene This is also observed in psychrotolerant yeasts which are progressively garnering awareness for their huge biotechnological capability. For example, antifreeze proteins which are crucial for tolerating freezing temperatures were reported for the first time in yeasts in Leucosporidium sp. AY30 (M. Trytek et al., 2005). Extracellular enzymes such as chitinase activity were indicated in Antarctic yeast isolates (Carrasco et al., 2012). The possible use of yeasts from Antarctica for bioremediation was also studied, as illustrated by Pichia caribbica that is capable of assimilating diesel fuel (Martorell et al., 2019). This research uncovers the potential of utilising Antarctica's yeast diversity for environmental cleanup efforts. The exploration of psychrotolerant yeasts has shed light on their immense biotechnological potential. From antifreeze proteins to extracellular enzymes and bioremediation capabilities, these organisms offer promising avenues for various industrial applications.

While psychrotolerant yeasts exhibit remarkable biotechnological potential, it is important to consider the production costs associated with psychrophilic yeasts, particularly in large-scale production practices. The culture of psychrophilic yeasts necessitates refrigerated conditions, which can significantly increase production costs. The consideration of production costs, including the requirement for refrigerated conditions, is essential in assessing the overall viability and scalability of utilising psychrophilic yeasts in industrial applications.

Psychrotolerant Fungi and Microbial transformation

One of the most studied whole-cell systems for microbial natural product isolation and for biotransformation are systems in fungi. Most active ingredients in medicine are inspired by natural products and the findings of this study would help improve current understanding in developing bioactive metabolites, providing the basis of more potent drugs via microbial transformation.

This is important as microbial transformation supports sustainable uses of resources under defined cultural conditions, freeing them from pathological restrictions and seasonal fluctuations. These microbial-catalysed reactions aid in generating diverse organic molecules with complex structures, such as steroids and boost the drug discovery process. Ethynodiol diacetate (1) is a semi-synthetic steroidal drug. It is a potent progestin that inhibits the ovulation process; therefore, it is used as an oral contraceptive.

Microbial biotransformation as a unique and inexpensive resource for bioactive natural products. The diversity of the possible reaction types in microbial transformation includes the processes of oxidation, hydroxylation, esterification, isomerization, reduction, acetylation, hydrogenation, and glycosylation.

Studies about the microbial transformation of diverse compounds provide a foundation for the role of fungi in modifying the chemical structure, libraries of analogue compounds with unique structural modifications can be generated by microbial biotransformation. This is due to fungal transformation of parent drugs or starting materials, which may result in the production of metabolites with structural similarities to the parent drug. Sustainable uses of resources under defined culture conditions are feasible via microbial transformation: unconstrained by seasonal fluctuations and pathological restrictions. These metabolites might be giving various metabolites from a single substrate enhanced pharmacological, pharmacokinetic, and toxicological properties on top of having comparable biological activities as parent drugs.

Recently, the fungal transformations of ethynodiol diacetate (1) were investigated in our lab using tropical (Botrytis cinerea, Trichothecium roseum) versus psychrotolerant fungus (R3-2 SP 17) The metabolites obtained include 17α-Ethynyl-17β-acetoxyestr-4-en-3-one-15β-ol (2), 19-nor-17a-ethynyltestosterone (3), and 17α-ethynyl-3β-hydroxy-17β-acetoxyestr-4-ene (4) Figure-1.

The use of psychrotolerant fungus as biocatalytic agent of 1 was reported here for the first time, resulting in a significant, improved yield of 3, and 4 than previous reported techniques. Among all the tested biotransformed compounds, the new biotransformed product, 2 is almost as potent as parent compound, 1 for anti-proliferative activity against SH-SY5Y tumour cell line. 3 has comparable acetylcholinesterase inhibition as 1. This is further supported by the binding mechanisms of 1, and 3 into the structure of rhAChE, which were examined through molecular docking studies. The activities reported here deserve to be taken into consideration as they are good illustrations, for supporting the application of microbial transformation as a viable method for future development of anti-proliferative drug candidates, and acetylcholinesterase inhibitors.

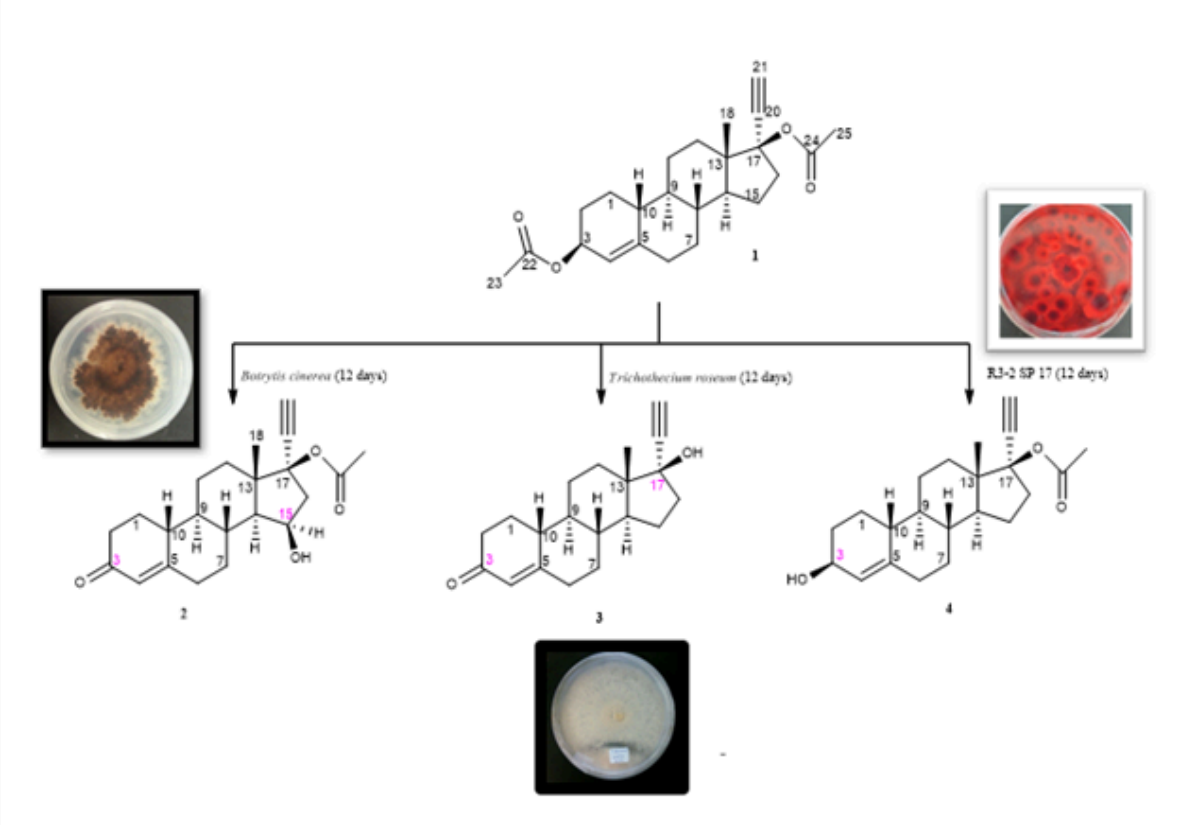


FIG.1. BIOTRANSFORMATION OF ETHYNODIOL DIACETATE (1) WITH BOTRYTIS CINEREA, TRICOTHECIUM ROSEUM, AND R3-2 SP 17

Over time, microbial transformation has emerged as a simple yet powerful tool for generating metabolites, playing a crucial role in strategizing bio-sustainable processes to accelerate the discovery of new drugs in the pharmaceutical industry. Thus, this research must be continued to cater to the growing demand for pharmaceuticals, on top of fulfilling the growing needs to live up to the commitment to the environment as advocated in Sustainable Development Goal 3: Good Health and Wealth-being of the 17 Sustainable Development Goals (SDGs), one of the United Nations 2030 Agenda for Sustainable Development. Additionally microbial transformation offers immense potential in the generation of valuable metabolites, which serve as essential building blocks for the development of novel pharmaceuticals. This approach not only enables the synthesis of complex compounds but also provides a sustainable alternative to traditional synthesis methods, minimising the use of non-renewable resources and reducing environmental impact.

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Assoc. Prof. Dr. Sadia Sultan obtained her Ph.D degree in 2004 from ICCBS Karachi University Pakistan. Then she worked as a chemist in the QA department of Abbott Lab Pakistan until April 2006. In June 2006, she was appointed postdoctoral at the Faculty of Pharmacy UiTM. Later in June 2009, she became a senior lecturer in the Department of Pharmacology and Pharmaceutical Chemistry at the Faculty of Pharmacy UiTM Puncak Alam. She has more than 20 years of experience in the field of natural product research. Her area of expertise includes:
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Exploring bioactive secondary metabolites from plant, soil and marine endophytic fungi. (using dereplication and OSMAC approach).
Modern NMR spectroscopic approaches in elucidation of secondary metabolites.

Questions

Let's dive deeper into the article and evaluate your comprehension. We have three questions for you here.

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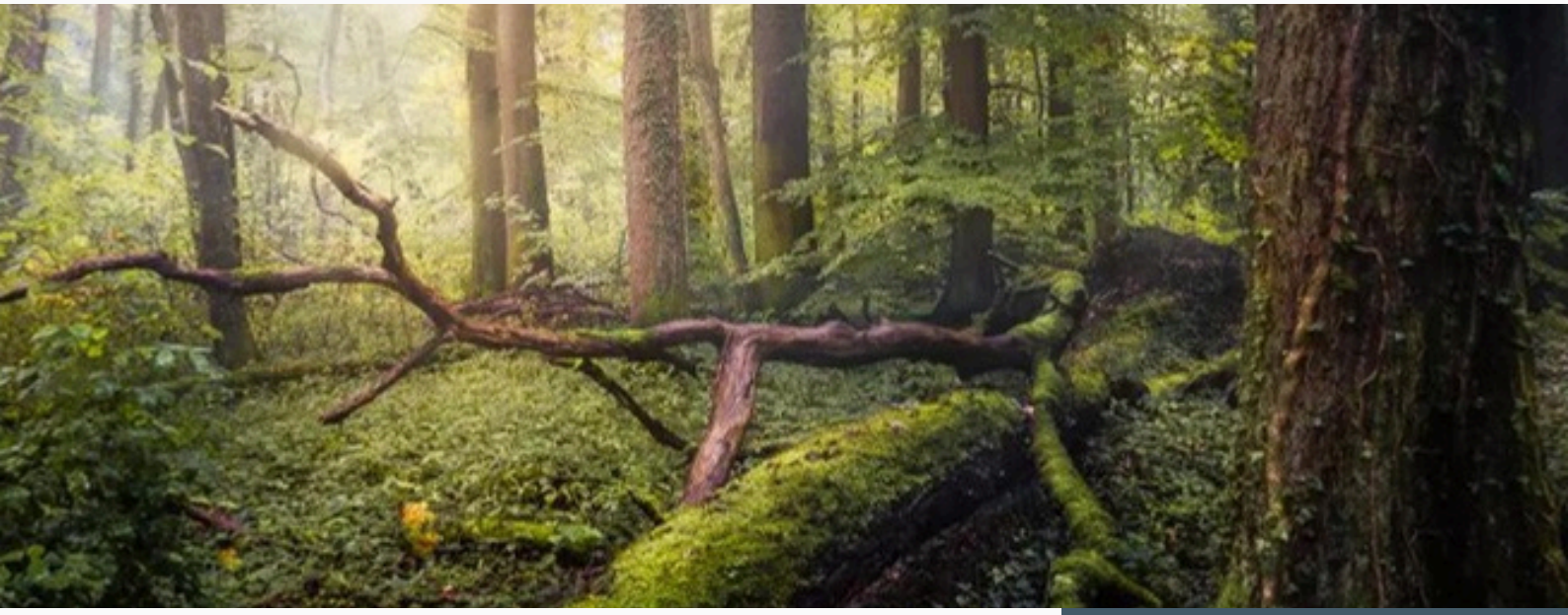

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