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MICROBIAL ENZYMES IN LIPID METABOLISM: UNVEILING THE KEY PLAYERS IN HEALTH AND DISEASE

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The current review investigates the role of microbial enzymes, particularly lipases and cholesterol oxidase, in lipid metabolism as well as their implications for health and disease. It highlights their role in releasing free fatty acids for energy and cell envelope synthesis, modulating host immune responses, and acting as potential therapeutic targets against intracellular pathogenic bacteria. Understanding their sources, purification techniques, and applications is crucial for advancing enzyme technology. An initial search for literature was done on different databases to obtain articles pertaining to the effects of microbial enzymes on lipid metabolism. They focused on these enzymes and their current understanding to highlight their general functionality in health and disease, as well as their innovative therapeutic significance. About them, the current and potential roles of lipids in lipid metabolism, the regulation of host lipid profiles, and their consequences for metabolic disorders were discussed. We conclude that microbial enzymes, such as lipases, cholesterol oxidase, and lipolytic enzymes, play a crucial role in lipid metabolism and human health. They influence cholesterol breakdown, fatty acid release, and bile acid synthesis, and they have therapeutic potential for metabolic disorders. Understanding and targeting these enzymes can lead to personalized therapies, drug development, and improved bioremediation strategies. Their multi-functionality extends to membrane structure, probing, and virulence

Keywords: *Microbial enzymes, Lipase, cholesterol oxidase, Lipid metabolism*

INTRODUCTION

Lipid metabolisms are essential to health and disease because of the functions that are associated with them, involving energy storage, structural components of cells, and signal transduction. Abnormal lipid metabolism is involved in such illnesses as atherosclerosis, diabetes, obesity, and other diseases[1]. Lipids' involvement in neurogenesis, in the formation of myelin sheaths, and their functioning as signal transducers puts them in the centrally important class of molecules[2]. In cancer, lipid metabolism changes have been associated with disease progression; thus, lipid omics is useful in the management of cancers[3]. Knowing the pattern of fat distribution can help to avoid various diseases and create precise treatments for patients[4]. Microbial enzymes are involved in the breakdown of lipids with the help of fatty acids that are required for certain functions in the human body. Lipases are microbial enzymes that catalyze the degradation of fats, improving energy generation and cell membrane formation [5,6]. These enzymes play a very central role in the digestion, absorption, and metabolism of lipids. Further, microbial lipases have valuable boundary uses, including in biodiesel production and in the pharmaceutical sector.

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This information assists in comprehending the fundamental correlation of microbial enzymes in lipid metabolic pathways and metabolic disorders, and hence the development of new therapeutic approaches in the treatment of disorders associated with lipid metabolism and fat storage [7,8]. The biochemistry of lipid metabolism is critical to human health and disease since it determines basic cellular processes. Lipids are important for cell membrane structure and as precursors for hormones, signs, and energy sources. Altered lipid metabolism is connected with life-threatening diseases such as obesity, cardiovascular diseases, diabetes, and cancer [9]. Decreased lipid synthesis or uptake may provide sustenance to cancer cells, and increased lipid deposition results in hyperlipidemia and visceral fat manifestation, which are associated with chronic diseases; furthermore, cardiovascular disease, type 2 diabetes, and nonalcoholic fatty liver disease. Knowledge of lipid metabolism is of great importance in designing effective prevention or management strategies for these diseases. Afterward, new studies focus on probable drug intervention objectives in lipid metabolism, underscoring the significance of lipid control for metabolic dysregulation and malignancy treatment [10,11]. Also, the contribution of the gut microbiome to lipid metabolism is examined, along with the progress in the development of microbiome-directed therapeutics. The development of efficient technologies such as lipid omics and mass spectrometry (MS) has improved the discovery of lipid signaling molecules and their biomarkers and our understanding of how lipid metabolites influence human health and disease conditions. Understanding the nature of lipid metabolism processes is important in order to provide people with individual diets as well as with individual therapeutic interventions[12,13]. Knowledge and recognition of microbial enzymes are important for the expected cures because of their high level of productivity, thermal resistance, and dexterity[14]. Microbial enzymes are extensively used in the synthesis of drugs and pharmacological agents such as thrombolytic agents, anticancer enzymes, and many more biotherapeutic agents. These enzymes include the following benefits like: low cost, large-scale production, and being selective against diseases like cancer, blood clotting, and genetic ailments. Investigations carried out on microbial enzymes have enabled the generation of enzyme-based therapies with higher efficiency and fewer side effects. Studying microbial enzymes provides new opportunities for research and development of new therapies; thus, it improves the possibilities of developing the concept of a personal approach to disease treatment and prevention [15,16]. In this review, we focus on a very critical aspect of lipid metabolism: the involvement of microbial enzymes, health and disease, and therapeutic targets. It aims to expand knowledge about how the composition of the microbiome within the gastrointestinal tract is connected with the host's lipid balance.

Role of microbial lipases in lipid metabolism

Microbial lipases are extracted from microbes such as fungi, bacteria, and yeast. These lipases are some of the most generalized biocatalysts, with unique enzymatic characteristics[17]. Lipases therefore facilitate the hydrolysis and synthesis reactions of ester compounds, making them potent in food and beverages, biofuels, textiles clothing, and apparel; cleaning agents and detergents; and pharmaceutical drugs. These include lipase (EC.3.1.1.3) and other enzymes, as they are involved in many reactions since they act as catalysts. Thus, it is necessary to mention that bacterial lipases often originate from *Pseudomonas* and have high activity and stability. Among lipases originating from extremophiles, lipases from halophiles are preferable for industrial use because of their characteristics such as thermos ability, pH optimality, salt tolerance, and versatility in various reactions[18,19]. EC.3.1.1.٨ denotes cholinesterase, an enzyme. Cholinesterase is an enzyme that hydrolyzes the neurotransmitter, acetylcholine, within the synaptic cleft, thereby inactivating its function. They are vital in the nervous system because of their contribution to the modulation of the level of acetylcholine and the pattern of neurotransmission [20]. In lipid catabolism and lipid digestion and absorption processes, microbial lipases are deemed to be very important. These enzymes can be divided into pancreatic lipase and bile-salt-dependent lipase, which catalyze the breakdown of dietary fats by splitting triglycerides into free fatty

acids and glycerol. Microorganisms that synthesize lipases are preferred due to economic considerations and the ease with which their enzymes can be constituted genetically [21]. These enzymes are widely used in industries such as food, detergent, cosmetics, and pharmaceuticals because of their general enzymatic functions. The use of microbial lipases is preferred in industries because they are stable, active, and more commercially viable than other sources of lipases [22]. Investigations have revealed the benefits of using extremophiles' lipases when undergoing biotransformation reactions, as the effects are improved yields accompanied by low byproducts. Furthermore, it is evident that cold-active lipases are useful in many industries because they are active at low temperatures and thus do not require extensive heating. The demand for lipases to be used in numerous biotechnological processes is expected to reach $590 million by the year 2023. In general, microbial lipases are essential global biocatalysts involved in the degradation and assimilation of lipids in numerous sectors and environmental uses [23,24,8]. Microbial lipases are involved in the metabolism of lipids and the functionality of adipose tissue in metabolic diseases such as obesity. Enteric lipases play a role in the digestion of ingested fats and their modulation of host metabolism regarding obesity [6]. Researchers have revealed that changes in the composition of the gut microbiota may influence the metabolic processes in hosts and thus affect weight shifts and lipid metabolism disturbances. The gut microbiota can alter energy extraction from the diet for lipid synthesis and effect the storage of triglycerides in adipose tissue, which are important parameters in obesity[22,25]. Furthermore, short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which are produced by the microbes, have been associated with the metabolism of adipose tissue, differentiation, lipolysis, and inflammation and consequently link microbial lipases to obesity pathogenesis. Thus, it is plausible to assume that the knowledge of how the microbial lipases and products formed in their course influence the processes occurring in adipose tissue and energy homeostasis may open up new approaches towards the prevention and treatment of obesity and its comorbidities[26].

Bile acid metabolism by gut microbes

Bile acids, which are synthesized in the liver, are absorbed in the intestines, where they undergo a vital conversion by means of microbial species, where primary bile acids are converted to the secondary forms of these acids, which play a great role in different pathways of metabolism in the human body. An impressive number of gut bacteria were observed to be involved in the biotransformation of primary bile acids derived from the host to the corresponding secondary bile acids by means of a series of oxidative reactions catalyzed by certain enzymes. These secondary bile acids have multiple effects on biological systems and may influence even the systemic metabolic condition [27]. Research has revealed that gut microbes have the capability of acquiring all enzymes involved in the modification of first-generation bile acids into second-generation bile acids with different physicochemical characteristics and functions [28]. The bacterial bioconversion of bile acids is in point form, that is, the transformation of these agents by different microbial types that participate in the biotransformation process in a step-wise manner, carrying out specific modifications at the molecular level on the bile acid molecules [29]. This change not only impacts host lipid, glucose, and energy status but also the composition of the gut microbiota due to its selective antimicrobial efficacy. The elucidation of the processes through which primary bile acids are transformed into secondary forms through the actions of gut microbes is important for explaining complex metabolic host-microbe interactions; it provides information on the possible management of metabolic diseases and other ailments[30]. Primary bile acid is involved in the systemic metabolism of the body: energy metabolism, glucose metabolism, and lipid metabolism. Primary bile acids are a part of cholesterol produced in the liver and function as hormones that bind to particular receptors located in the liver, intestine, adipose tissue, and pancreas. An example of the mentioned receptors is the farnesoid X receptor (FXR), which is mainly located in the liver and intestine. Bile acid binding to FXR modulates

the genes that are related to the synthesis, transport, and catabolism of bile acids and glucose and lipid metabolism. Stimulation of FXR also helps in the conversion of cholesterol into bile acids and thereby in the regulation of lipid livor in the liver. Bile acids also activate the Takeda G protein-coupled receptor 5 (TGR5) that is present in different tissues, such as the intestinal tract, adipose tissue, and muscles too. TGR5 activation by bile acids induces the release of other hormones, for example, glucagon-like peptide-1(GLP-1), which has a positive effect on insulin secretion and glucose handling. Moreover, TGR5 receptor activation enhances energy spending and stimulates the process of 'brite' or brown-like differentiation of white adipose tissue for the sake of improving the metabolic profile [31,32]. TGR5 receptor is a G protein-coupled receptor with specific innate bile acids distributed through tissues and organs. It affects how energy is produced and used, the management of glucose levels, inflammation, and liver activity. The agonist of TGR5 enhances the individual's tolerance to insulin, increases energy consumption, suppresses inflammatory processes, and acts against liver diseases, so it can become a drug target [33]. Also, it remains to be noted that bile acids can change the structure and activity of the gut microbiota, which, accordingly, influences the total metabolism. Bile acids are capable of passing through the gastrointestinal tract (GIT), and hence, the gut microbiota is capable of converting them to secondary bile acids that have different effects on the metabolism. It is shown that changes both in gut microbiota composition and in the levels of bile acids are connected with the development of metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), and nonalcoholic fatty acid liver disease (NAFLD). Thus, it can be concluded that the changes in bile acid metabolism strongly affect overall systemic metabolism. Using specific receptors and affecting the gut microbiota, bile acids participate in energy, glucose, and lipid balance. Knowledge of the difference and interconnection between system bile acid metabolism and bile acid metabolism can contribute to the advancement of new treatments for metabolic diseases[34,35]. Hence, modulation of bile acid metabolism is known to have large therapeutic potential in different metabolic and liver illnesses. Bile acids, being not only the crucial elements in the digestion process, also act as the hormone-sensitive lipase-labile factors that are involved in the regulation of energy intake and expenditure, glucose, and lipid homeostasis via specific receptors, such as farnesoid X receptor and TGR5[36]. Bile acid homeostasis disturbances have been described in chronic liver diseases, and thus, molecules modulating bile acids, bile acid transporters, and bile acid synthesis regulators[37]. Interventions that modulate bile acid metabolism or signaling, including bile acid receptor agonists, could be a new strategy for obesity and diabetes treatment [38]. Furthermore, the treatment of bile acid also provides promising evidence as a viable avenue in the management of type 2 diabetes mellitus concerning glucose tolerance, insulin sensitivity, and energy metabolic disorders [39]. Other synthetic bile acid derivatives, like obeticholic acid, have had beneficial outcomes in clinical metabolic and hepatobiliary diseases [35]. By elucidating how bile acids are metabolized and integrated with systemic metabolism, one can hope for the development of new approaches to treat metabolic disorders, liver diseases, and other states with dysregulation of bile acids. Especially strains belonging to *Lactobacillus*, bacteria play key roles in the gut and metabolic health due to their ability to modify and neutralize bile salts. Some of the prototypes include *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus gasseri* which influence the bile salt bacterial growth by deconjugation. Other bacteria, including *Bacteroides* and *Clostridium*, are also involved in dehydroxylation, where they transform primary bile acids to secondary ones. It is important not to over transform our bodies because dysbiosis and related diseases are brought about by it[40,41].

Microbial cholesterol oxidase and its role in lipid metabolism

Microbial cholesterol oxidase is a useful enzyme that has a variety of applications on the commercial market and plays a significant part in many processes occurring in living organisms. This enzyme is quite widespread among different microorganisms and has medical importance, contributing to the

catabolism of cholesterol, bacterial virulence, and the synthesis of antifungal antibiotics [42]. In commerce, cholesterol oxidase finds tremendous application in testing cholesterol in clinical samples, being employed in the food industry, and it might be used in pest control [43]. They include biocatalysis, where it is used in synthesizing steroids and in the detection of cholesterol in clinical samples and foods. Thus, it can be stated that the enzyme has great commercial potential due to its potential use in such fields as pharmaceuticals, agriculture, and biotechnology[44,45]. Chemically, microbial cholesterol oxidase has the biochemical activity that works for cholesterol oxidation and isomerization; it results in the formation of hydrogen peroxide and cholesteric 4-ene-3-ketone. Other biological uses of this enzyme include more than just the breakdown of cholesterol; however, there are other uses in clinical diagnoses, medical treatment, and biopesticide production. With the knowledge of the commercial importance and biological functions of microbial cholesterol oxidase, there are possibilities for its applications in different fields and industries and reorganization of its relevance in scientific studies and in real life [46]. Cholesterol metabolism is a complex process involving enzymatic pathways that are essential for maintaining cellular homeostasis and human health. It primarily occurs in the endoplasmic reticulum through a series of reactions, with 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase being a key regulatory enzyme. Cholesterol can be obtained from the diet or synthesized in cells[47]. Enzymatic pathways are tightly regulated to prevent excess accumulation or depletion of cholesterol, which could lead to various diseases. Cholesterol metabolism is also interconnected with the synthesis of steroid hormones, bile acids, and other bioactive molecules. Enzymatic pathways also play a crucial role in the breakdown of cholesterol, such as cholesterol being converted into bile acids in the liver. Understanding these pathways offers insights into cholesterol regulation, lipid-lowering drug development, and cholesterol imbalance management [48]. Microbial cholesterol oxidase is a versatile enzyme with a wide range of applications across various industries. It is used in clinical laboratories for cholesterol analysis, medical diagnostics, therapeutic development, the food industry, agriculture, the pharmaceutical industry, and biotechnology. In clinical laboratories, it is used for cholesterol analysis, biosensor detection, and lipid profile assessment. In the food industry, it is used for food quality control, biocatalysis, insecticidal activity, and bioremediation[49,50]. In agriculture, it has potential as an insecticide due to its enzymatic properties. In the pharmaceutical industry, it plays a crucial role in steroid drug production and antibiotic production. In biotechnology, researchers have engineered mutant variants of cholesterol oxidase with enhanced properties, such as improved thermos ability. Recombinant enzyme production is another area where microbial cholesterol oxidase plays a significant role. Understanding the enzymatic properties of cholesterol oxidase can contribute to the development of novel therapeutic strategies for managing cholesterol-related disorders [51-53].

Impact of gut microbiota on lipid metabolism

The gut microbiota is well established to be a critical component in lipid metabolism in the host, with implications for numerous parameters of wellbeing and pathology. It is associated with diet lipids, mediating with the host's physiological aspect by means of metabolism and growth repression. Alterations of the gut microbial composition are associated with dyslipidemia and diseases resulting from it, such as non-alcoholic liver disease and atherosclerosis. For instance, short-chain fatty acids and secondary bile acid that originate from the gut microbiota have been understood to impact lipid homoeostasis in the host [54,55]. It alters the lipid content in liver and plasma cholesteryl esters and cholesterol; overall, the gut microbiota influences lipid metabolism. All these affect triglyceride levels, lipid clearance in serum, adipose tissue, and liver, and similarly, the lipid species in serum, adipose tissue, and liver. The depletion of gut microbiota in the mice decreases several genes that are responsible for cholesterol and fatty acid synthesis in the liver, hence decreasing the hepatic lipid stores[56,57]. Commensal microbes influence cholesterol and bile acids in the gut, modulating metabolic activities and predisposing individuals to diseases. It also

modulates the manifestation of lipid content in the liver and affects genes associated with cholesterol and fatty acid metabolism. It influences cholesterol homeostasis and therefore has a therapeutic application in the regulation of hypercholesterolemia[58,59]. Therefore, the gut microbiota modulates lipid metabolism in the host through metabolism regulation, lipid profile change, cholesterol management, and the composition of the microbiota. Appreciation of these interactions would be instrumental in determining the place of the gut microbial ecosystem in metabolic health and disease [60,61]. Thus, the gut microbes have functional interactions with the host for lipid metabolism, ultimately modulating the host's health and disease. They form metabolites such as short chain fatty acids and secondary bile acids that affect host lipid metabolism, influencing cholesterol biosynthesis as well as intake [62,63]. These metabolites can influence the liver and plasma blood lipid profiles and cholesterol, as well as lipid species. Bacteria in the gut also control hepatic genes that are involved in cholesterol and fatty acid synthesis, which determine lipid storage and processing in the liver. Alterations of gene expression that are associated with lipid metabolism can, in turn, alter lipid utilization and storage in the host. Knowledge of these mechanisms is crucial to designing effective therapies that will enhance the metabolic profile of lipids and overall metabolic health [53,64]. The targeting of gut microbiota can be regarded as a prospective therapeutic target for different diseases because microbiota significantly affects the host metabolic processes and immune system and can contribute to the development of certain diseases [65]. Obesity and metabolic disorders can cause positive energy balance, which has a hint that this can help to reverse the problem and therefore presents a new horizon in the prevention and treatment of these diseases. It has been ascertained that most participants reported metabolic changes through non-surgical interventions comprising diet modification, antibiotic treatment, and fecal microbiota transplantation. Patients' microbiota modulates response to cancer therapies and toxicity, and fecal microbiota transplantation has been shown to have potential in the management of the disease in clinical trials. Changing the composition of the gut microbiota can improve immune responses against tumors and minimize tolerance to cancer treatment. This understanding could bring drastic changes in the management of diseases and the results achieved in the process[66,67].

Future directions and therapeutic implications

In the context of lipid metabolism, lipases, a class of microbial enzymes, are vital. These enzymes increase the rate of hydrolysis of lipids into fatty acids and glycerol, which are involved in several biochemical processes. They have also reported the various roles of microbial lipases in the management and utilization of lipids, energy production, and cell metabolism. Lipases can be defined as highly active enzymes that are of widespread use in various industries, such as biodiesel, food processing, detergent, and pharmaceutical industries. The source of the microbial origin of lipases has some benefits, such as reduced production costs and the ability to bioovercome the enzymes genetically. New studies were devoted to the analysis of the structural and functional characteristics of lipases, working on their enhancement of production and their application in various kinds of industries [8, 68-70]. Future research in understanding microbial enzymes could include metagenomics and enzyme discovery using shotgun metagenomics, protein engineering techniques to enhance existing industrial enzymes, computational enzyme modeling to understand complex enzymatic mechanisms, biocatalytic remediation for sustainable pollution mitigation, and structural studies to uncover the mechanistic basis of enzymatic reactions, substrate specificity, and binding mechanisms for improved enzyme design and optimization. These research directions aim to expand our knowledge of microbial enzymes and their applications in various fields, contributing to the development of more effective and efficient enzymes[21,71-74]. Microbial enzymes give indications that they could be useful as therapeutic agents for metabolic syndrome. It is involved in gut microbiota-host interactions and influences glucose tolerance and metabolic pathways[75]. Peculiar features of enzymes, the improvement of which is possible through

protein engineering, include new types of therapeutic actions and medical uses. Manipulating bacterial enzymes and their metabolites may affect the processes that take place in the body, for this reason, they are considered possible therapeutic targets[76,77]. A strategy to improve our knowledge of the links between the gut microbiome and metabolic diseases is know-how that results from microbial enzymes and aims at providing new approaches to their treatment [78].

Conclusion

Thus, we can deduce that microbial enzymes play a pivotal role in lipid metabolism, as it affects human health through cholesterol degradation, the release of fatty acids, and bile acid synthesis. They have medical usability in metabolic diseases and are important biomolecules with applications in biodiesel production, among others. Knowledge and manipulation of these enzymes present novel approaches to the management of lipid-related disorders. Microbial enzymes also affect the drug, metabolism, gut health, and immunological responses, which indicate the general health of an individual. Studies or investigations carried out on microbial enzymes are gradually shifting towards personalized therapies, novel drugs, and more efficient bioremediation techniques. Subsequent research involves the discovery of particular enzymatic procedures involving the consumption or production of probiotics and human microbiome species, as well as their general effects on health. The number of enzymes to be discovered is large, largely summarized as ‘omics’ approaches that are required for OMICs approaches for high-throughput bioprocesses. Gut microbial enzymes are known to forecast human disorders, and this is comprehensible.

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الإنزيمات الميكروبية في عملية التمثيل الغذائي للدهون: الكشف عن اللاعبين الرئيسيين في الصحة والمرض

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تتناول هذه الدراسة المرجعية دور الانزيمات التي تنتجها الميكروبات، خاصة الليبيز وأكسيديز الكوليسترول، في ايض الدهون بالإضافة إلى آثارها على الصحة والمرض. كما تسلط الضوء على دور هذه الإنزيمات في تحرير الأحماض الدهنية الحرة لتوليد الطاقة وبناء أغشية الخلايا، وتعديل الاستجابات المناعية للمضيف، والعمل كأهداف علاجية محتملة ضد البكتيريا المسببة للأمراض داخل خلايا المضيف. وبالتالي، فإن فهم مصادر هذه الإنزيمات وتقنياتها واستخداماتها أمر بالغ الأهمية لتطويرها تقنيًا. تم إجراء بحث أولي في قواعد البيانات المختلفة للحصول على مقالات تتعلق بتأثير الإنزيمات الميكروبية على استقلاب الدهون. وتسلط النتائج الضوء على هذه الإنزيمات وفهمها الحالي، مع تسليط الضوء على وظيفتها العامة في الصحة والمرض وأهميتها العلاجية المبتكرة. كما تمت مناقشة الادوار الحالية والمحتملة لهذه الانزيمات في عملية التمثيل الغذائي للدهون، وتنظيمها لملف الدهون لدى المضيف وتأثيرها على اضطرابات التمثيل الغذائي. نستنتج أن الإنزيمات الميكروبية، مثل الليبيز وأكسيديز الكوليسترول والإنزيمات المحللة للدهون، تلعب أدوارًا مهمة في استقلاب الدهون وصحة الإنسان. كما انها تؤثر على تحلل الكولسترول وإطلاق الأحماض الدهنية وتخليق الأحماض الصفراوية ولها إمكانات علاجية لاضطرابات التمثيل الغذائي.، كما يمكن أن يؤدي فهم دور هذه الإنزيمات ودراستها إلى استكشاف علاجات وتطوير أدوية وتحسين استراتيجيات المعالجة البيولوجية.