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Review Article

# Unlocking the Clinical Significance of Cytochrome P450 Enzymes

**Rajesh Hadia*, Vishal Singh, Nidhi Solanki, Shiwanand Sharma, Varunsingh Saggu, Cyril Sajan, Rahul Trivedi, Sunil Kardani, Sunil Baile, Hemraj Singh Rajput, Rajesh Maheshwari**

Department of Pharmacy, Sumandeep Vidyapeeth (Deemed to be University), Vadodara, Gujarat, INDIA.

## ABSTRACT

**Aim/Background:** The Cytochrome P450 (CYP) enzyme family, consisting of 57 distinct genes, plays a pivotal role in various biological processes. These genes encode enzymes with multifaceted functions, impacting vital processes like arachidonic acid metabolism, xenobiotic detoxification, eicosanoids production, and drug metabolism. Moreover, CYP enzymes are indispensable for the synthesis of bile acids, steroids, and numerous metabolic pathways. They also participate in the hydroxylation of retinoic acid, illustrating their remarkable versatility. While some CYP enzymes still have undiscovered functions, their role continues to captivate researchers across diverse domains. Additionally, mutations in CYP genes can give rise to inborn metabolic disorders, leading to clinically significant diseases, underscoring the importance of CYP enzymes in maintaining metabolic equilibrium and overall well-being. Beyond their initial association with hepatic drug detoxification, recent research has unveiled a broader spectrum of enzymatic processes undertaken by cytochrome P450. The complexity of CYP enzymes is progressively unfolding, emphasizing their clinical significance and opening new avenues for drug development, precision medicine, and patient care. **methodology:** This abstract presents a comprehensive overview of the literature on cytochrome P450 enzymes and their diverse functions. The information was gathered from a wide range of sources, including scientific articles, textbooks, and research publications. The analysis covers the genetic basis of CYP enzymes, their roles in various metabolic pathways, and the clinical implications of CYP gene mutations. Additionally, the abstract highlights the recent advances in our understanding of CYP enzymes and their expanding role in maintaining human life. **Results:** The results of this study showcase the remarkable diversity of functions performed by cytochrome P450 enzymes. They are intricately involved in processes critical to human health, ranging from drug metabolism to the synthesis of vital biomolecules. The study underlines the clinical significance of CYP enzymes, as mutations in these genes can lead to severe metabolic disorders and diseases. Furthermore, it emphasizes the evolving understanding of CYP enzyme complexity and its implications for drug development, precision medicine, and patient care. **Conclusion:** In conclusion, this abstract sheds light on the exceptional versatility and clinical importance of cytochrome P450 enzymes. Their diverse functions have far-reaching consequences for human health, making them a focal point of research in pharmacology and medicine. The evolving understanding of CYP enzyme complexity paves the way for future advancements in drug development and personalized patient care, offering new possibilities for enhancing the well-being of individuals and populations. This research underscores the significance of CYP enzymes and their potential to revolutionize the fields of medicine and pharmacology.

**Keywords:** Cytochrome P450, Drug Metabolism, Clinical Significance.

**Correspondence:**
**Dr. Rajesh Hadia**
Assistant Professor, Department of Pharmacy Practice, Sumandeep Vidyapeeth (Deemed to be University), Vadodara-391760, Gujarat, INDIA.
Email: docrajesh.hadia@gmail.com

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## INTRODUCTION

Since its original identification in 1961, Cytochrome P450 (CYP) has emerged as a pivotal milestone in the history of scientific research. The peculiar designation P450 was given to this cellular chromophore because it exhibits a spectacular 450 nm spectral peak when examined in a reduced state when bound to carbon monoxide. As research developed until the middle of the 1960s, CYP's real complexity started to emerge, demonstrating its crucial function in drug metabolism and steroid production. CYP was initially thought of as a single enzyme during the early 1960s. The late 1970s saw intriguing hypotheses of the existence of numerous P450 enzymes emerge as the scientific community dug deeper into the mysteries of CYP. However, revealing the entire fabric of this enzyme system proved to be a difficult task. The hydrophobic nature of CYP, which is embedded in cellular membranes and hinders straightforward purification, makes it

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difficult to determine the specific number of proteins involved. This process of learning, characterized by early excitement, progressive revelation, and continuing hurdles, illustrates the ongoing intrigue and significance of Cytochrome P450 in the field of biology and medicine. In this introduction tale, we begin a historical investigation of CYP, a protein whose intricate nature continues to fascinate researchers and holds the potential to provide deep new understandings of fundamental biochemical processes and their clinical ramifications. A critical period in the study of cytochrome P450 (CYP) occurred in the early 1980s, which helped to spark important developments in the discipline of molecular biology. Gonzalez and his colleagues successfully isolated the first complete cDNA encoding a cytochrome P450 protein during this transformative era, which contributed to the advancement of mRNA purification techniques.[1] This accomplishment paved the way for a deeper investigation of the CYP family and opened the door to a new world of opportunities. In addition to confirming the existence of numerous CYP enzymes, later cloning research also revealed the enormous diversity present in this family of proteins. Fascinating discoveries were made through the comparative examination of their sequences, which showed startling parallels between the cytochromes P450 present in humans and bacteria. These similarities suggested the existence of a shared ancestor gene that dates back around three billion years.[2] Such findings highlighted the crucial function of CYP enzymes in fundamental biological processes and its deep evolutionary significance. A systematic classification system was created more than 15 years ago in response to the growing understanding of the complexity of the CYP family. This naming approach, which was founded on the ideas of divergent evolution, intended to scientifically classify and name the different CYP enzymes. This nomenclature system is dynamic and is constantly being improved and expanded through online platforms, guaranteeing that our knowledge of CYP enzymes keeps up with the rapidly expanding field of molecular biology.[3,4] These advancements not only reflect important turning points in the study of CYP but also demonstrate how collaborative and dynamic scientific research is as it reveals the mysteries of this amazing enzyme family. This nomenclature system is dynamic and is constantly being improved and expanded through online platforms, guaranteeing that our knowledge of CYP enzymes keeps up with the rapidly expanding field of molecular biology. These advancements not only reflect important turning points in the study of CYP but also demonstrate how collaborative and dynamic scientific research is as it reveals the mysteries of this amazing enzyme family.

Based mostly on the degree of amino acid sequence similarity, the classification of Cytochrome P450 proteins into separate families and subfamilies offers a highly effective and methodical methodology. This approach helps to categorize these enzymes thoroughly by making the naming system more organized and approachable. Enzymes that display at least 40% sequence identity are categorized into distinct families, each of which is denoted by an Arabic number. This classification makes it easier to comprehend the evolutionary connections and functional traits that enzymes in the same family share. In addition, subfamilies are formed for enzymes that have a stronger degree of sequence similarity, often at a threshold of 55% or higher. This level of categorization granularity enables a more exact discrimination between closely related enzymes, frequently revealing subtle functional variations. The Cytochrome P450 nomenclature organizes the vast and complicated world of CYP proteins in a systematic and hierarchical manner, simplifying the complex terrain of these enzymes while also giving researchers and scientists a framework to work within.

This strategy emphasizes the value of sequence-based classification in helping us better understand the roles and purposes of these crucial proteins. Let's look at two well-known examples to show how useful this classification method is: the sterol 27-hydroxylase and Vitamin D3 24-hydroxylase enzymes. These enzymes belong to the same CYP27 family because they share a considerable amount of sequence similarity-at least 40%. However, by identifying separate subfamily names based on the level of sequence similarity, the approach improves precision. Due to less than 55% commonality in their protein sequences, vitamin D3 24-hydroxylase and sterol 27-hydroxylase are classified as CYP27A and CYP27B, respectively.

This naming scheme is particularly strong since it is flexible enough to accommodate new discoveries. If, for example, another enzyme were to appear that shared at least 55% of the sequence with sterol 27-hydroxylase, it would naturally be given the name CYP27A2, maintaining a steady and orderly progression. This methodological approach has successfully reduced the naming-related ambiguity that is frequently present in gene families and super families. In addition to fostering clarity and precision in communication, establishing a well-structured system for the classification of Cytochrome P450 enzymes also makes it easier to grasp their various roles within the scientific community. As a result, the nomenclature system has evolved into a crucial instrument in the field of molecular biology, facilitating the classification and identification of these vital proteins.[1,2] There are already more than 270 different Cytochrome P450 (CYP) gene families, 18 of which have been shown to exist in mammals, making the landscape of CYP gene families nothing short of comprehensive.[4] Given the enormous variety of tiny molecules present in the world of plants, this astounding diversity should not come as a surprise. It was anticipated that plants would have a large number of cytochrome P450 enzymes,[5,6] and when the genome of the little mustard plant Arabidopsis thaliana was examined, this prediction was verified. A startling total of 249 active CYP genes and 24 non-functional pseudogenes were found in Arabidopsis thaliana, accounting for an amazing 1% of the plant's total number of genes. At least 324 functional CYP genes have also

been found in equal numbers in the rice genome.[4] However; the human genome only has 57 CYP genes and 33 pseudogenes, which is a striking difference. There are 42 subfamilies and 18 families in which these genes fall. Unless new active members of the CYP2G and CYP2T subfamilies are discovered, which could potentially increase the existing number; it is important to note that large changes to this count are unlikely. This discrepancy in CYP gene representation levels between species emphasizes the distinctive genetic traits and functional requirements inherent to each creature.[7] The CYP gene families' extreme diversity and complexity illustrate the fascinating connection between genetics and the myriad biological mechanisms that control many animals. We learn more about the processes governing metabolism, adaptability, and the evolution of life on Earth as we delve deeper into these varied genetic landscapes.

Our understanding of P450 enzymes has been fundamentally altered by advances in molecular biology and genetics, which cast doubt on the idea that these enzymes are principally involved in the liver's metabolism of drugs. First of all, by catalyzing a variety of reactions on a wide range of endogenous substrates, these enzymes have demonstrated amazing adaptability. A wide variety of substances, including fatty acids, eicosanoids, sterols, steroids, bile acids, retinoids, and uroporphyrinogens, are transformed by these enzymes through oxidative, peroxidative, and reductive processes. Furthermore, P450 enzymes demonstrate the ability to metabolize a wide range of exogenous substances, including medications, contaminants, and natural chemicals obtained from plants, demonstrating their adaptability to varied molecular configurations.[4,5] P450 enzymes can also produce potentially hazardous by-products, which can increase the risk of cancer, birth abnormalities, and other toxic effects, even though they frequently detoxify foreign substances. The buildup of particular substrates can also cause the expression of a variety of P450 enzymes. For instance, relevant P450 enzymes are activated to effectively digest and remove the extra substrate when certain chemicals build up in the liver.[8,9] These discoveries deepen our understanding of P450 enzymes and demonstrate the diverse functions they play in both health and sickness. These results demonstrate the diversity of cytochrome P450 enzymes and the importance of their role in the metabolism of a wide variety of exogenous and endogenous chemicals. Understanding the functions of these enzymes in both typical physiological processes and pathological situations is crucial because of the complicated interactions that these enzymes have with the numerous substrates that they bind to. This wide viewpoint is crucial for understanding the complexity of biological systems and developing targeted treatments for both health and illness.

The expression of human CYP3A enzymes can be induced by the consumption of medications like rifampicin, which is frequently administered for bacterial infections. In addition to speeding up the metabolism of rifampicin, this induction also causes other medications that depend on CYP3A enzymes for their breakdown to be eliminated from the body more quickly. Rifampicin also affects a number of CYP2C enzymes, which causes the elimination of drugs processed by these enzymes to happen more quickly. When one P450 substrate affects the concentrations and metabolism of another, the phenomenon known as drug interactions results, complicating treatment regimens.[10] Individual cytochrome P450s have a variety of biological and clinical roles, and the availability of cloned genes and the subsequent creation of biochemical and immunochemical probes derived from these cDNAs have shed light on their different biological and clinical functions. The metabolism of endogenous substrates and the synthesis of hydrophobic lipids including cholesterol, bile acids, steroid hormones, and fatty acids are both crucially dependent on these enzymes. We give a brief review of the physiological functions performed by numerous human cytochrome P450s below, along with how those functions may affect clinical outcomes. This information sheds light on the complex interactions that exist between these enzymes and physiological functions in the body, which ultimately affect how diseases develop, how drugs work, and how patients fare as a whole. It is essential to comprehend these intricate relationships in order to improve patient care and therapeutic approaches.

The cytochrome P450 enzymes play a crucial role in the metabolism of eicosanoids, arachidonic acid, and exogenous compounds. Foreign chemicals, also known as xenobiotics, include drugs, secondary metabolites from plants or fungi consumed through food, as well as different environmental pollutants like halogenated hydrocarbons, polycyclic aromatic hydrocarbons, arylamines, combustion by-products, industrial mixtures, herbicides, and pesticides. The CYP1, CYP2, CYP3, and, to a lesser extent, CYP4 family of cytochrome P450 enzymes are principally responsible for metabolizing these foreign substances within the human body. It's important to note that each of these gene families has a large number of allelic variants, which results in pharmacogenetic variation between people. These genetic variants alter the efficacy and safety profiles of medications by influencing how individuals metabolize and react to xenobiotics. Cytochrome P450 enzymes are essential for the metabolism of arachidonic acid and eicosanoids in addition to their function in the metabolism of foreign chemicals. These lipid mediators are essential for controlling physiological processes like inflammation, vascular homeostasis, and others. Arachidonic acid is metabolized by cytochromes P450 of the CYP2 and CYP4 families, which produce eicosanoids such prostaglandins and leukotrienes that control a variety of cellular functions. The intricacy of inter individual variations in medication response, vulnerability to environmental toxins, and overall health outcomes is highlighted by the occurrence of allelic variants within the gene families implicated in metabolizing foreign compounds and lipid mediators. Understanding the effects of genetic differences in cytochrome P450 enzymes is essential for

directing personalized medicine techniques, enabling customized pharmacological regimens, and minimizing potential side effects. An substantial database of human CYP gene allelic variations is available online, offering a consistent classification scheme to aid in this understanding.[11] Both scholars and doctors can benefit from this database as a beneficial tool. The consensus or reference sequence, designated as the (*1 allele) within this classification scheme, often reflects an efficient-metabolism phenotype. The poor metabolism phenotype, on the other hand, is typically encoded by variant alleles and is characterized by reduced or absent enzyme activity toward particular medicines. A variant genotype may occasionally represent an ultra-metabolism phenotype with extremely high enzyme activity as a result of gene duplications. It is critical to understand that individual variations in these genes can have a big impact on how drugs work and how they are metabolized. The rates of ambient chemical detoxification and metabolic activation can also range significantly amongst people with various CYP haplotypes. Particularly among people with an efficient metabolism or high activity phenotype, some CYP enzymes, including CYP1A1, CYP1A2, CYP1B1, CYP2D6, CYP2E1, CYP3A4, and CYP3A5, have been related to an increased risk of certain types of cancer or harmful consequences. These effects can also be made worse by the co-inheritance of other polymorphic enzymes that are involved in the same metabolic pathway as the medication or chemical.[12-18] Despite the strong evidence provided by animal research, it is still extremely difficult to confirm these correlations in clinical populations. The crucial function of cytochrome P450 enzymes in regulating individual reactions to medications and environmental exposures is nevertheless highlighted by these studies, opening the door for more specialized and efficient medicinal interventions.

In order to implement personalized medicine strategies, it is essential to comprehend the effects of genetic polymorphisms in the Cytochrome P450 (CYP) genes. This will help medical professionals choose the best drugs, alter their dosages, and assess the likelihood of adverse responses. The intricate interactions between genetic diversity, medication metabolism, and individual responses are gradually becoming clearer because to ongoing research and advancements in genomic medicine, which ultimately improve patient care and treatment outcomes. A member of the CYP gene family, CYP1 is notable for being predominantly controlled by the polycyclic aromatic hydrocarbons (PAHs)-activated aryl hydrocarbon receptor, a transcription factor. Smoke from cigarettes, charcoal-grilled meals, and industrial incineration products are all common sources of these PAHs. While CYP1A2 primarily metabolizes arylamines and N-heterocyclics, CYP1A1 and CYP1B1 of the CYP1 gene family show variable expression levels across organs and effectively metabolize PAHs. Interestingly, an unexplained endogenous ligand for the aryl hydrocarbon receptor is metabolized by CYP1A1, CYP1A2, and potentially CYP1B1.[19] Additionally, CYP1A1 has the ability to inactivate prostaglandin G2, whereas CYP1A2 and CYP1B1 play different roles de the hydroxylation of estrogen at the carbon-2 and carbon-4 locations, respectively. Additionally, CYP1A2 participates in the metabolism of melatonin and helps to oxidize uroporphyrinogen.[20-22] Comparatively, CYP1A1 and CYP1B1 are not predominantly drug-metabolizing enzymes, but CYP1A2 demonstrates metabolic activity toward about 10-20 distinct medications. Although the causes of the higher expression of CYP1B1 in some solid tumors are yet unknown,[23] this finding may present prospects for the development of chemotherapeutic therapies. The ability of all three CYP1 enzymes to detoxify or activate different environmental carcinogens is significant. Understanding the complex roles and controls of the CYP1 gene family can help us better understand how PAHs, arylamines, endogenous ligands, and other substrates are metabolized. Understanding the mechanisms underlying their participation in solid tumors offers up the possibility of using these enzymes for specialized treatment approaches. The CYP1 enzymes' extensive detoxifying and activation capacities show their importance in protecting human health by underscoring their critical role in managing environmental toxins. Intriguing results have been obtained from extensive research with animals lacking the Cyp1a1, Cyp1a2, and Cyp1b1 genes. These mice continue to live despite changes in drug and carcinogen metabolism, indicating functional redundancy or non-essential functions for these enzymes in the metabolization of endogenous substances.[24-26] The precise roles and contributions of these enzymes in typical physiological processes are called into doubt by these discoveries in compelling ways. Contrarily, primary congenital glaucoma, also known as buphthalmos, has been linked to mutations in the human CYP1B1 gene.[27] This clinical finding shows that CYP1B1's metabolism of an essential endogenous substrate is necessary for the correct development of the anterior chamber of the eye during embryogenesis. Given that CYP1B1 is involved in the synthesis and breakdown of retinoic acid,[28] it is conceivable to assume that this route contributes to the genesis of primary congenital glaucoma. It is still unclear how the overlapping substrate specificities of CYP1A1 and CYP1A2 interact with the retinoic acid pathway. The complicated relationships within this biological network are highlighted by the fact that mice with a defective Ahr gene, relevant to this debate, show liver retinoid buildup and impaired retinoic acid metabolism. These fascinating findings raise questions about the specific roles and interactions of the CYP1 gene family in healthy physiology as well as disease processes. Further investigations are essential to elucidate the specific roles of these enzymes in various pathways, including retinoic acid metabolism, and to gain a comprehensive understanding of their significance in human health and development.[29]

The largest P450 family in mammals and home to the widest variety of enzymes with a variety of roles is the CYP2 gene family. In particular, numerous members of this family of human

enzymes, including CYP2C8, CYP2C9, CYP2C18, and CYP2C19, play crucial roles in the metabolism of more than half of the medications that are often prescribed, as well as other compounds including arachidonic acid and certain steroids. More than 75 medications are believed to be metabolized by CYP2D6 according to *in vitro* research.[15] Different medications are also metabolized by other family members, including CYP2A6, CYP2A13, CYP2B6, CYP2E1, CYP2F1, and CYP2J2.[30,31] The roles of other members, including CYP2A7, CYP2R1, CYP2S1, CYP2U1, and CYP2W1, are currently unknown. While the CYP2C subfamily of enzymes are predominantly involved in the metabolism of drugs, there is evidence that a CYP2C enzyme, stimulated by -naphthoflavone, contributes to the vascular endothelium's synthesis of the vasodilator 11,12-epoxyeicosatrienoic acid.[32] The majority of CYP gene products in vertebrates presumably initially developed for critical life tasks before obtaining the capacity to breakdown plant compounds and metabolize medicines, according to this study that emphasizes a recurrent topic in P450 research.[8] The CYP2G and CYP2T subfamilies appear to be pseudogenes in humans, despite the fact that they encode functional genes in rodents. This suggests that whatever purposes these genes may have served during the mammalian radiation some 80 million years ago are no longer required in humans. Notably, mice lacking the Cyp2e1 gene appear normal on the outside but have remarkable resistance to benzene toxicity,[26] highlighting the role of this subfamily in xenobiotic metabolism. These findings highlight the CYP2 gene family's amazing diversity and complexity, with its considerable contributions to drug metabolism and potential significance in a number of physiological processes. The particular roles of the uncharacterized members must be revealed, and their consequences for human health and disease must be better clarified, through ongoing research.

The four members of the CYP3 gene family are CYP3A4, CYP3A5, CYP3A7, and CYP3A43. These include the highly expressed CYP3A4 and CYP3A5, which are essential for the metabolism of over 120 regularly prescribed medications[12-17] as well as endogenous substrates such steroids and bile acids.[33,34] They play an important clinical role in the metabolism of some antifungal and immunosuppressive medications. When given the recommended amount, those with a poor-metabolizer phenotype might experience excessive drug concentrations, whereas people with an extensive-metabolizer phenotype might have poor metabolism of these medications, resulting in inadequate drug levels. Further research on the involvement of hepatic CYP3A43 in drug metabolism is necessary because its function is not fully understood. While CYP3A7 is expressed in the uterine endometrium and fetal liver, its precise roles in these tissues are still understood. A key route controls the expression of CYP3A enzymes in the liver and gut.[35] The expression of members of the CYP3A family has been demonstrated to be induced by a number of medications, and the degree of induction by a specific molecule can differ between species.[36,37] Pregnane X Receptor (PXR), a transcription factor that is ligand-activated and a member of the nuclear hormone receptor superfamily, mediates this induction. PXR interacts with particular DNA patterns or response elements in the regulatory regions of CYP3A genes to bind to small molecules and stimulate the transcription of those genes. The capacity of a substance to engage in interaction with the ligand-binding region of the PXR receptor can be used to explain differences in the induction of CYP3A enzymes between species.[38,39] The ability of some medications to shield organisms from the hazardous effects of other chemicals is explained by this regulatory mechanism and its pharmacological features.[40] For instance, pregnenolone derivatives can reduce the hepatotoxicity brought on by consuming drugs like indomethacin and digitoxin. These pregnenolone-related chemicals function as PXR ligands, causing the creation of CYP3A enzymes, which then render dangerous drugs inactive. The active ingredient in St. John's wort, hypericum, activates the PXR and CYP3A genes in a manner similar to this, enhancing the metabolism of a variety of substances, including prescription medicines and the negative consequences linked to them.[41] In addition to PXR, the Constitutive Androstane Receptor (CAR), a different member of the nuclear hormone receptor superfamily, can also stimulate several CYP2B and CYP3A genes. It has been found that CAR can activate CYP3A genes through PXR response elements, and PXR can control CYP2B genes through the CAR or phenobarbital response element, despite the regulatory elements or DNA patterns in the regulatory regions of these genes being different for CAR and PXR.[42,43] This interaction of receptor transcription factors provides an additional line of defence against the negative effects of hazardous substances, including those present in plants. Predicting drug-drug interactions and developing new therapies can both benefit greatly from an understanding of the mechanisms behind drug metabolism and the regulatory pathways including PXR and CAR. PXR and its target genes, including the CYP3A enzymes, can be used in screening techniques that could help us better understand possible drug interactions and create treatments that work better.

CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4F22, CYP4F22, CYP4A20, CYP4A22, CYP4V2, and CYP4X1 are the 12 members of the CYP4 gene family. Even though some of these genes play a part in the metabolism of drugs, their main function is in the metabolism of fatty acids, such as arachidonic acid, leukotrienes, prostaglandins, Epoxyeicosatrienoic acids (EETs), Hydroxyeicosatetraenoic acids (HETEs), and Hydroperoxyeicosatetraenoic acids (HPETEs). Particularly, CYP4F8, CYP4F11, CYP4F12, and CYP4F22 are connected to the metabolism of fatty acids and arachidonic acid (7). CYP4A20, CYP4A22, CYP4V2, and CYP4X1 are currently thought to have uncertain roles (43). The distal convoluted tubules of the kidney express a number of CYP4A and CYP4B enzymes. Alterations in salt metabolism, water balance, and arterial blood pressure can result from defects in particular CYP4 genes.[44] It's

important to note that human kidney enzymes like CYP4A11 and CYP4F2 have also been identified to convert arachidonic acid to 20-HETE,[45] even though research on blood pressure regulation has mostly been done in rats.

In addition to the cytochrome P450 enzymes' roles in the metabolism of pharmaceuticals and foreign substances, arachidonic acid serves as a substrate for a number of these enzymes.[8] Prostaglandins D2, F2, and E2 as well as Epoxyeicosatrienoic acids (EETs), Hydroxyeicosatetraenoic acids (HETEs), and Hydroperoxyeicosatetraenoic acids (HPETEs) are among the over 100 eicosanoids metabolites produced as a result of arachidonic acid metabolism. These eicosanoids play a role in a variety of physiological processes, including the contraction of smooth muscle, edema formation, intestinal vasodilation, allergic reactions, chemotaxis, inhibition of platelet aggregation, bone resorption, the production of fever, the mobilization of intracellular calcium, the modulation of sodium and potassium ATPase, egg formation, and angiogenesis.[46,47] It is very likely that there are disorders caused specifically by mutations in the P450 enzymes involved in the metabolism of arachidonic acid, even if these diseases have not been thoroughly characterized. Notably, thromboxane A2 synthase (CYP5A1) and prostacyclin synthase (CYP8A1), two distinct P450 enzymes, perform opposite roles in blood clotting. Thromboxane A2, which is made by CYP5A1, lowers the level of cyclic AMP in platelets and encourages platelet aggregation. Prostaglandin I2 (prostacyclin), on the other hand, is produced by CYP8A1 and increases intracellular cyclic AMP levels while preventing platelet aggregation. Therefore, it is expected that mutations in the CYP5A1 or CYP8A1 genes may cause clotting and inflammatory disorders, including illnesses like coronary artery disease and pulmonary hypertension.[48,49]

Several cytochrome P450 enzymes work together to metabolize cholesterol and produce bile acids. At least seven, and maybe nine, P450 enzymes are involved in this complex process that turns acetate into sterols and bile acids. The CYP51A1 gene encodes lanosterol 14-demethylase, an essential enzyme in the production of cholesterol. By using oxidative processes to remove two methyl groups from the intermediate molecule lanosterol, this enzyme is essential for the creation of cholesterol. Notably, antifungal medications like ketoconazole target lanosterol 14-demethylase. Surprisingly, this enzyme is highly conserved in a wide range of species, including animals, fungi, plants, and even the prokaryote Mycobacterium TB. Due to its extensive distribution, it has been hypothesized that this enzyme may be the ancestor of all eukaryotic cytochrome P450 enzymes.[4,50,51] A important catabolic mechanism for cholesterol removal in animals is the formation of bile acids from cholesterol. The metabolic transformations are catalysed by a variety of cytochrome P450 enzymes from distinct families, including CYP3, CYP7, CYP8, CYP27, CYP39, and CYP46. For instance, CYP7A1, CYP7B1, and CYP39A1 start the production of bile acids by adding a hydroxyl group to the carbon-7 of the B ring in the substrates cholesterol and oxysterol. A nuclear hormone receptor called the farnesoid X receptor (FXR) controls the CYP7A1 gene. Bile acids, cholesterol, triglycerides, and proatherogenic serum lipoproteins are all increased in Fxr-deficient mice.[52] The major bile acid cholate is produced by the sterol 12-hydroxylase CYP8B1.[53] Involved in the production of oxysterol and the oxidation of the sterol side-chain, CYP27A1 functions as a sterol 27-/26-hydroxylase.[54] Additionally, CYP46A1 takes involvement in the synthesis of oxysterols.[55] Because it is primarily expressed in central nervous system neurons, CYP46A1 stands apart within the P450 superfamily. This enzyme changes cholesterol into a particular oxysterol called 24S-hydroxycholesterol, which, unlike cholesterol itself, may easily pass the blood-brain barrier. Because it is transformed by the liver into bile acids, 24S-hydroxycholesterol production and excretion into the bloodstream are essential for maintaining healthy levels of cholesterol in the brain. They also help with reverse cholesterol transport. Multiple P450 genes involved in the production of bile acids have had mutations discovered and characterized. Hypercholesterolemia and medication resistance to cholesterol-lowering statins are caused by CYP7A1 gene dysfunction.[56,57] A male infant's severe hyperoxysterolemia was shown to be caused by a CYP7B1 gene mutation.[58] Additionally, cerebrotendinous xanthomatosis, a hereditary condition marked by accelerated atherosclerosis and severe neurological impairment, has been linked to approximately 50 distinct mutations in the CYP27A1 gene. Cholic acid, which aids in restoring the bile acid pool and preventing the formation of harmful sterol intermediates within the bile acid pathway, can be used to treat CYP27A1 deficiency.

Several cytochrome P450 enzymes work in concert to synthesize and process steroids, particularly in the early embryonic phases of sexual differentiation. The nuclear hormone receptor gene family member steroid-factor-1, a transcription factor, is essential for upregulating P450 genes, which include those from the CYP11, CYP17, CYP19, and CYP21 families and are involved in the manufacture of steroid hormones.[59] A trio of enzymes called CYP11A1, CYP11B1, and CYP11B2 are found in the mitochondria. Cortisol, testosterone, and estrogen are all produced by the enzyme CYP17A1, while androgenic precursors are changed into estrogens by the enzyme CYP19A1. The endoplasmic reticulum contains the genes CYP17A1 and CYP19A1. CYP17A1 is a dual-purpose enzyme that can catalyse both the cleavage and oxidation of the side chains of steroid substrates as well as the 17-hydroxylation of those same substrates. Deficits in the generation of glucocorticoids and sex hormones are caused by mutations in CYP17A1 that affect these enzyme functions. However, shortages in sex hormones alone are caused by mutations that specifically stop oxidation and side chain shortening. Lipoid adrenal hyperplasia is brought on by CYP11A1 mutations, whereas 11-hydroxylase insufficiency is brought on by CYP11B1 errors. Corticosterone methyl oxidase

type I deficiency or corticosterone methyl oxidase type II deficiency are caused by allele-specific mutations in CYP11B2. Glucocorticoid-remediable aldosteronism is brought on by recombination of the closely related CYP11B1 and CYP11B2 genes on chromosome 8, which encode functional chimeric enzymes.[60,61] By aromatizing the A ring of androgenic steroid substrates, CYP19A1 produces estrogen. The importance of estrogens in bone development is highlighted by the possibility that loss-of-function mutations in CYP19A1 can cause or manifest skeletal problems. Males who have uncommon gain-of-function mutations in CYP19A1 may develop gynecomastia.[62] A important stage in the production of glucocorticoids and mineralocorticoids is the hydroxylation of steroid precursors at carbon-21, which is carried out by the enzyme CYP21A2. Over 90% of cases of congenital adrenal hyperplasia, a common genetic condition, are caused by disruptions in the 21-hydroxylation process. Classic congenital adrenal hyperplasia, simple virilizing congenital adrenal hyperplasia, and non-classic congenital adrenal hyperplasia are the three main classifications of this disorder based on clinical presentation and severity. While mild virilizing congenital adrenal hyperplasia largely causes excessive virilization without the severe salt-wasting symptoms, classic congenital adrenal hyperplasia manifests with life-threatening symptoms such salt wasting and masculinization of females. In non-classical congenital adrenal hyperplasia, CYP21 activity is only slightly impaired. Congenital adrenal hyperplasia can also result from mutations in other steroidogenesis-related genes, such as CYP11A1, CYP11B1, CYP11B2, CYP17A1, and CYP19A1. Each of these genes is essential for the production of different steroid hormones. Congenital adrenal hyperplasia can be developed as a result of disruptions in their function, which can change hormone production.[63-66]

The CYP26 gene family, which comprises of three genes from distinct subfamilies and suggests a shared history going back at least 150–200 million years, mediates the essential process of retinoic acid hydroxylation. Each of these genes produces the enzymes needed to hydroxylate retinoic acid, a kind of vitamin A. One of these, CYP26A1, is only able to metabolize all-trans retinoic acid and is not capable of doing so with 9-cis or 13-cis retinoic acid. During the development of vertebrates, retinoic acid functions as a crucial morphogen, acting through a variety of retinoic acid receptors and retinoid X receptors. CYP26A1 may act as a catabolic enzyme for vitamin A, similar to many other cytochrome P450 enzymes involved in drug metabolism. CYP26A1 may control and reduce the powerful developmental signals mediated by retinoids by degrading the ligand for retinoic acid receptors. It is yet unclear exactly how CYP26B1 and CYP26C1 contribute to the metabolism of retinoic acid or the processing of its products. To understand the precise biological actions these enzymes take in relation to retinoic acid metabolism, further study is required.[7]

Future research on CYP gene products is expected to reveal a growing number of functions that they have in many biological systems. High levels of polymorphism are present in the CYP superfamily genes, which is a trait shared by the majority of genes in the human genome. Inter-individual changes in phenotype caused by this genetic variability within the P450 enzymes will have a profound impact on medicine and treatment modalities. Numerous investigations will soon reveal links between particular CYP variant alleles and a variety of genetic disorders, environmental toxicities, cancer, and other complicated diseases, it is predicted. These studies will help us comprehend the complex relationship between genetic variables and illness vulnerability better. Such discoveries have enormous potential for personalized medicine since they can lead to customized treatment plans based on each person's particular genetic makeup. It is critical to recognize that the area of genetics is always evolving and that new developments and discoveries will probably keep happening. Therefore, new knowledge about the wide and varied functions of CYP enzymes will surely become available in the future, influencing our understanding of human health and directing potential therapeutic approaches.

## CONCLUSION

The CYP gene families, which comprise CYP2, CYP3, CYP4, and CYP26, are essential to human biology since they function in several aspects such as drug metabolism, fatty acid processing, steroid production, and control of retinoic acid. Significant variability in CYP2 enzymes affects individual responses, and these enzymes are essential for the metabolism of drugs and other substances. Members of the CYP3 family, such as CYP3A4 and CYP3A5, are critical for drug metabolism; however, different genetic variants can result in different pharmacological effects. The main physiological function of CYP4 genes is the metabolism of fatty acids, which helps control blood pressure and other bodily functions. Development is impacted by the CYP26 family's involvement in the metabolism of retinoic acid. Additional roles and connections between CYP gene variations and genetic illnesses, environmental reactions, and complex diseases are anticipated to be uncovered by future study. These findings enable customized treatments based on individual genetic profiles, which has significant implications for personalized medicine. These gene families' genetic diversity reveals the complex interactions between chemicals, genes, and human health, opening up new and intriguing possibilities for our knowledge of human biology and the development of therapeutic interventions.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**CYP:** Cytochrome P450; **DNA:** Deoxyribonucleic Acid; **RNA:** Ribonucleic Acid; **mRNA:** Messenger Ribonucleic Acid; **cDNA:** Complementary DNA; **CYP2G:** Cytochrome P450 2G; **CYP2T:** Cytochrome P450 2T; **PAHs:** Polycyclic Aromatic Hydrocarbons; **N-heterocyclics:** N-heterocyclic compounds; **CYP1A1:** Cytochrome P450 1A1; **CYP1A2:** Cytochrome P450 1A2; **CYP1B1:** Cytochrome P450 1B1; **Ahr:** Aryl Hydrocarbon Receptor; **HETEs:** Hydroxyeicosatetraenoic Acids; **EETs:** Epoxyeicosatrienoic Acids; **HPETEs:** Hydroperoxyeicosatetraenoic Acids; **FXR:** Farnesoid X Receptor; **PXR:** Pregnane X Receptor.

## SUMMARY

Cytochrome P450 (CYP) enzymes, with 57 distinct genes, are crucial for various biological functions, including drug metabolism, synthesis of essential compounds, and maintaining metabolic balance. Mutations in CYP genes can lead to serious health issues. Recent research has unveiled their broader roles, expanding possibilities for drug development and personalized medicine. Understanding CYP enzyme complexity is revolutionizing pharmacology and medicine.

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