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# Review article: Cytochrome P450 from discovery to pandemic

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***Abstract*---**Discovery of the new drug or evaluation of chemical moiety which possesses drug like properties are need to be check for cytochrome P450 studies. Cytochrome P450 (CYP450) enzymes responsible and involved in variety of biochemical reaction. It plays vital role in detoxification of xenobiotics (Drugs, foreign particles, toxins etc) with the help of metabolism processes. It also has important function for the synthesis of various messengers or hormones. *In vitro* CYP450 studies responsible for the determination of pharmacokinetics parameters like half-life and clearance of drugs. Inhibition of CYP450 and induction of CYP450 undergoes drug-drug interaction. Concomitant medication can induce or inhibit the CYP450, resulting in drug adverse reaction. Interindividual efficacy of drug and disease susceptibility depends on the genetic polymorphism in CYP gene. During the drug discovery process, experiments designed set to check the metabolism of drug by various isoforms of CYPs like CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4 associated metabolism. Novel COVID-19 disease progress due to multiplication of SARS-CoV-02 viruses in the human's body and transmit to other person by contaminated droplets. Since it is novel disease, mortality rate high due to lack of evidenced based clinical studies. However, literature suggest comorbidity and cytochrome strome due to virus infection could be the cause of high mortality rate, mainly by affecting the expression of CYP450. In the present review highlights are cytochrome functions in normal and disease condition. Comprehensive compilation of cytochrome associated activity in metabolism, drug discovery and alteration in the CYP expression level during disease condition. Review gives the insights of medication used during the treatment of COVID-19 infected patient through repurposing approach. Proposed mechanism of mortality during the pandemic could be because of toxicity associated with concomitant medication and comorbidity. Hence cytochromes involved in all stages of drug discovery and recently the pandemic (COVID-19 disease) mortality observed due to altered expression of cytochrome P450 level.

***Keywords*---**Cytochrome P450, Drug discovery, inflammation, cancer, COVID-19.

## Introduction

Cytochrome P450 (CYP450) an enzyme responsible for numerous clinical and pathophysiological conditions. It mainly involved in the biotransformation reactions and ultimately associated with effect and side effects of drug. CYP450 enzymes possesses variety of biochemical reaction, detoxification of xenobiotics (Drugs, foreign particles, toxins) etc. with the help of metabolism mainly redox reactions. Pharmacokinetics parameters are mainly derived with the help of *invitro and invivo* studies, emphasize on cytochrome associated depletion of drugs.(Zanger & Schwab, 2013a) It also has important function for the synthesis of various messengers or hormones to maintain the homeostasis. Expression of cytochromes are associated with variety of tissues in the human body, like- liver, lung, kidney, intestine, adrenal cortex etc.(Girirajan et al., 2011) Based on the structure presence of iron in cytochrome P450 enzymes are able to metabolise large number of molecules.(Morris et al., 2015) Large number of factors like nutraceuticals, dietary molecules, environment condition and comorbidity effect the mechanisms of action of CYP isoenzymes. Wide involvement of CYPs involved in inflammation condition, disease and also seen in recent pandemic of COVID-19 patients.(Deb & Arrighi, 2021a)

## Cytochrome P450 primer

Cytochromes are called as CYP P450 based on the chromophore absorb UV-light at 450nm hence the name is given as cytochrome P450. Different variety of CYPs identified in various sources as per literature. Cytochrome P450 enzymes found in abundant number of species, like mammal, plants, yeasts, virus, insects and Monera.(Lamb et al., 2009) More than 300,000 P450 sequence identified recently in living creatures. In bacteria >62,000 CYPs, >85,000 fungal CYPs. More than 13,000 named P450s in animals and plants have over 16,000 CYPs(Nelson, 2009). Haemoproteins CYP450 involved in metabolism and detoxification of xenobiotics. Drug metabolism takes place with the help of seven important enzymes: CYP 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4(Zhao et al., 2021). Most abundance CYP enzymes substantial ones are CYP3A4 and CYP2D6.(Veith et al., 2009) Hepatic metabolism mostly takes place with the help of CYP3A4 and intestine express CYP3A5, both are involved in extrahepatic metabolism.(Lynch & Price, 2007) Majority of phase I drug metabolism reactions are carried out through cytochromes. Cytochromes P450 mostly associated with the phase I metabolism reactions like- oxidation, reduction, hydrolysis, dealkylation, epoxidation and dehalogenations, etc(Zhao et al., 2021). Abundant level of cytochrome enzymes associated with liver are involved in metabolism of drug substances fatty acid metabolism and steroid/drug/ xenobiotics metabolism and catabolism of exogenous compounds(Food and Drug Administration, 2017). Pharmacokinetic parameters are derived from different studies, however CYP 450 associated studies produce half-life and clearance of drugs. Hence, Clearance of drug related with the toxicity profile of the drug.(Guengerich, 2021; Tyzack, 2019) Drug fate govern by polymorphisms in the CYP family. CYP 2D6, 2C19, and 2C9 polymorphisms responsible for variations in phase I metabolism of drugs in individuals; around 80% of drugs metabolized by CYP enzymes. CYP 2D6 activity lack in ~ 5–14% of Caucasians, 0–5% Africans, and 0–1% of Asians, and such individuals are known as poor metabolizers.(Biotransformation, n.d.)

Another clinically significant enzyme CYP 2C9 demonstrates multiple genetic variants with a potentially functional impact on the efficacy and adverse effects of drugs that are mainly eliminated by this enzyme.(Zanger & Schwab, 2013b) The distribution of the common variant alleles of CYP genes varies among different ethnic populations(Manuscript, 2012). New investigational drug and marketed drug both efficacy and safety improve with the pharmacogenetics.(Veith et al., 2009; Zanger & Schwab, 2013a)

**Cytochrome in healthy state**

In the healthy human liver verity of transporters, cytochromes enzymes are responsible for the absorption of nutrition and detoxification of toxins. Cytochromes are distributed not only in liver but also in other body organs and play vital role. Phase I (redox reactions) and Phase II (conjugation reaction) reactions are associated with the homeostatic balance of the body.(Nebert et al., 2013)Metabolic reaction controls the reactive species generation, covalent binding, toxin accumulation and toxin removal from the body and ultimately healthy functioning of organs.

**Cytochrome in disease state**

Cytochrome relates to clinical condition of human beings, since other enzymes, genes and mutations are associated with life functions hence pathology variable effect seen in the population.(*CYP-Cancer Diabetes Atherosclerosis.Pdf*, n.d.) Protection starts with cascade of reaction of inflammation, bodies have its own programmed defence mechanism, activates in recognition by foreign particle, damage cells, toxins and pathogens. Inflammation reaction happening with the help of molecular mediators, immune cells and blood vessels. Steps to repair damage start with recruitment of inflammatory mediators at the cellular damage, eliminate damaged or necrotic cells and finally tissue repair initiate. Various inflammatory signs like pain, swelling, redness and heat produced by inflammatory mediators at the site of injury. Innate (cellular) and adaptive (acquired for specific pathogen) immunity are the components of inflammations. Acute and chronic inflammation are classes of inflammation, acute inflammations is the immediate response to stimuli and chronic inflammation is the prolonged inflammation, leads to multitude of diseases.(Stavropoulou et al., 2018).

Inflammation is the repair process and if unable to happen properly will leads microbial invasion to damage tissue leads to infection. Cascade of reaction of inflammation starts with activation of cytokines, enzymes like proteases, adipokines, lipid metabolites nitric oxide and ROS (reactive oxygen species).(Nebert et al., 2013) Mechanism of inflammation comes with reduction of enzymes system involved in the metabolism CYP isoenzymes at liver and adipose tissues. Mainly Inflammatory mediators include vasoactive amines histamine, proinflammatory cytokines (IL-1β, IL-6, and TNFα), lipid mediators (i.e., prostaglandins) and peptides (i.e., bradykinin)(Zhou et al., 2006). Host repairing process start with stimulation of toll like receptor and inflammation promoters will target the injure site and promotes removal of microbial cells. As the inflammatory signal received, liver tissue start increase secretion and synthesis of CRP (C- reactive protein), alpha acid glycoproteins etc, those involved in the body

balance system. Infection modulates the function of liver by modulating the metabolism enzymes, and ultimately pharmacokinetics of the drug. Liver is the major organ of metabolism, modulation of liver enzyme expression due to infection disturbance of hepatic clearance.

Inflammation associated infection can cause alteration in drug transporters proteins and drug metabolising enzymes of liver and intestinal epithelial cells, hence resulting in modification of oral bioavailability. CYP enzymes and cytokines regulations are interrelated, hence CYP enzymes involved with different inflammatory conditions thus pharmacokinetics will be affected after drug administration and infection states. Downregulation of CYP enzymes occurs at different inflammatory stages, observed by altered level of mRNAs as transcription is the mechanism of protein synthesis. In inflammation NF-κB play key regulatory factor. NF-κB p65 subunit bind to retinoid X receptor (RXR) and regulate the action of pregnane X receptor (PXR).(Gu et al., 2006) Aryl hydrocarbon receptor binding with NF-κB result in suppression of their activity. Decrease level of hepatic and extrahepatic CYP enzymes associated with inflammation altered the plasma level of drug and metabolites adverse effect.

**Cytochrome in Drug discovery and development**

Cytochrome P450 involved in the variety of transformation reaction. At the drug development stage invitro cytochrome P450 enzyme associated metabolism, to check the route of disposition, effect on transport and verify the potential of drug-drug interaction.(*In Vitro Drug Interaction Studies-Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Guidance for Industry*, 2020)

Metabolism of drug takes place in variety of organs, like liver, kidney, lung, skin, intestine wall etc, however liver and intestine are the major sites. These two organs abundantly express variety of metabolism enzymes and involved in lot of biotransformation reactions.(Chung et al., n.d.) Liver associated CYP isoenzymes involve in phase I reactions. (Oxidation, reduction and hydrolysis).(Zhao et al., 2021) Apart from CYPs other phase I enzymes are also involved in the metabolism like aldehyde oxidase (AO), carboxylesterase (CES), flavin monooxygenase (FMO), xanthine oxidase (XO), monoamine oxidase (MAO), and alcohol/aldehyde dehydrogenase (ADH/ALDH).(Thompson, 2009) UDP glucanosyl transferases (UGTs) and sulfotransferases (SULTs) are the phase II reaction enzymes.(Stresser et al., n.d.) Some of non CYP involved reactions are also involved in the metabolism of drugs. Inhibition and induction of CYP enzymes due to concomitant medication leads to drug- drug interaction.(Hakkola et al., 2020) New investigational drugs need to evaluate as substrate, inhibitor or inducer of metabolizing enzymes for assessment of safety profile. List of known substate, inducer and inhibitor also published.(Food and Drug Administration, 2017) As per US-FDA guideline circulatory metabolite exposer should not be more than 10% of total drug exposer, hence its mandatory to evaluate the metabolism pathway of newly investigated drug along with the quantification of circulatory metabolites.(*In Vitro Drug Interaction Studies-Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Guidance for Industry*, 2020; Thompson, 2009)

**Cytochrome in COVID-19 Pandemic**

As COVID-19 novel disease, SARS-CoV-2 (Severe Acute respiratory Syndrome Coronavirus) main causative organism of COVID-19 disease.(Lenoir et al., 2021) WHO mentioned the occurrence of COVID-19 is the public health emergency of international alarm condition on 11 March 2020 and was declared as pandemic. (Deb & Arrighi, 2021b)As COVID-19 pandemic is the novel disease, hence standard treatment for the disease not finalize yet due to lack of research and clinical trials. Initially started with antimalarial drug chloroquine and hydroxychloroquine which restrict the entry of corona virus and ultimately viral load.(Deb & Arrighi, 2021b; Smit et al., 2020; Zahr et al., 2021) Antiviral drug remdesivir mainly used for Ebola virus infection was introduced. Currently corticosteroid dexamethasone along with some of the oxygen measures used for the management of patient's conditions.(Hodge et al., 2020) Neutralizing Monoclonal antibody (mAb) discovery underway to get the breakthrough treatment for the COVID-19 infection, some of the pharma companies working to get the monoclonal antibodies to decrease the virus load and prevent from further damage.(Cruz-Teran et al., 2021; Perlin et al., 2022; Rubin, 2022; Verderese et al., 2022) Based on the finding related to toxicity associated with the decrease cytochrome P450 expression, future work needed to formulate drug with safety profile without CYP inhibitor activity, to decrease the toxicity associated mortality of COVID-19 infected patients.(Rodriguez-Morales et al., 2020)

Mortality due to COVID-19 complication include anaphylactic shock, respiratory system failure, acute respiratory distress syndrome (ARDS), thromboembolism, multiorgan failure like heart, liver, kidney and existing disease condition like diabetes, heart diseases etc.(Bierle et al., 2022; Demopoulos et al., 2020) Mortality seen due to multiorgan damage with inflammation mainly seen on liver.(Kumar & Trivedi, 2021) The main effect of inflammation associated decrease expression of liver cytochrome P450 enzyme and subsequent effect on drug metabolism.(Wang et al., 2022) Invitro study with hepatocytes has shown that increase lode of cytokines in inflammation, inhibit the cytochrome isoenzymes expression. Decrease expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 isozymes observed due to inflammatory mediators like IL-6.(El-ghiaty et al., 2020) As the isoenzyme's expression decrease, metabolism of concomitant medication will decrease and subsequently associate with the toxicity. Toxicity seen in patients mainly because of drug-drug interaction and drug used for comorbidity.

**Conclusion**

Cytochrome P450 covers the plethora of drug discovery to the COVID-19 pandemic. It plays vital role for safety and efficacy of drug. Along with effects it has important role in bacterial/viral pathogenesis. Regulatory authority, toxicologist and pharmacologist always give importance to cytochrome associated studies. Pharmacokinetic modification due to concomitant medication seen due to inhibition or induction of cytochrome. Cytochrome expressions level are important to establish the effective and safe medication therapy; also challenge the virus/ bacterial attack.

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