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Review

Implications of Drug Metabolizing Enzyme System in Pharmacological Actions of Drugs.

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Keywords: Drug metabolising enzymes, MFOS, CYP, Drug-drug interactions, pharmacogenetic polymorphisms.

Abstract: In this review the implications of drug metabolising enzyme system known as Mixed Function Oxidise System (MFOS) and its components, with special reference to the role of cytochrome P450 (CYP) in pharmacological actions of drugs is discussed. CYP enzyme family has received attention for drug development because of its diversified functions of metabolising wide variety of substances including pharmaceutical agents. Various aspects such as interactions of CYP with xenobiotics which include drugs and environmental pollutants and with naturally occurring compounds, drug-drug interactions and polymorphism play a role in modulating the rate of MFOs , which determine the pharmacological action of the drug. The relationship between dietary fat type and metabolism xenobiotics is important in deciding the biological fate of the drugs and carcinogen pollutants. An account of interactions of imidazole drugs with MFOS components such as CYP and epoxide hydrolase is presented. The understanding of the interactions of endogenous drug substrates of CYP and antifungal imidazole drugs is imperative in drug development for skin diseases. The discussion pertaining to the current knowledge and emerging concepts in the area of drug metabolism in context of CYP encompasses the perceptive of using CYP enzymes in drug synthesis for selective oxidation and applications of bacterial and genetically engineered CYP variants. An insight in to the mechanism of drug-drug and drug-herb interactions, the newer understanding of pharmacogenic polymorphism and the novel applications of CYP will contribute to the development of safer and more efficient therapies.

1. Introduction

The foreign compounds or xenobiotics (exogenous chemicals), which we are exposed to, do not play any physiological role in normal metabolism. These compounds include pharmacologically active agents which enter into the body by design or as well as , chemicals such as carcinogens, pesticides, insecticides, vehicular and industrial emissions and other environmental pollutants, which enter inadvertently. Thus the ‘defence system’ basically developed by the body to eliminate the xenobiotics, also

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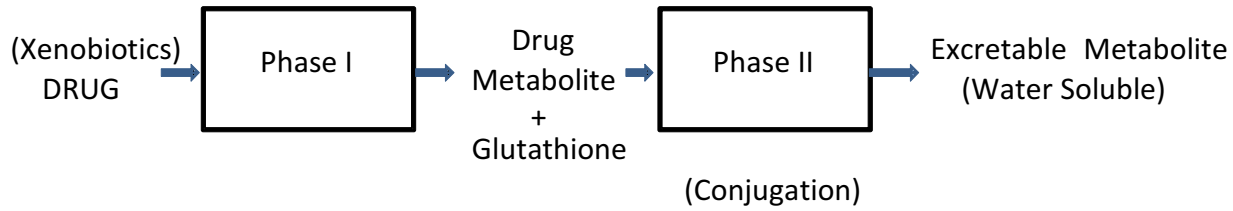
metabolizes the drugs and in turn gets affected by the xenobiotics entering in to the bio system. This changes the rate of drug metabolism [1-3].

An enzyme system capable of oxidizing xenobiotic compounds was identified in the endoplasmic reticulum of the liver and was designated as Mixed Function Oxidase System (MFOS). Metabolic fate of xenobiotics including drugs is determined by the hepatic microsomal MFOS, which is the site of interactions among these foreign compounds [4]. This allows drug-drug and drug-chemical interactions [5]. The large variety of microsomal enzyme catalyse oxidative, reductive, hydrolytic and glucouronidation reactions [6,7]. Although liver is the principal organ for drug metabolism, MFO activities associated with drug and carcinogen metabolism are also distributed within extrahepatic tissues such as lungs, gastrointestinal tract, kidneys and skin[8,9]. The MFOS components are inducible by certain drugs such as bar-biturates [10].

Drug metabolism is the biochemical modification of pharmaceutical substances by living organisms and its rate is an important determinant of the duration and intensity of the pharmacological action of drugs [11- 13]. The metabolism of the drug, in general, consists of two phases defined as phase-I and phase-II. Phase-I includes the reactions resulting in the incorporation of a polar reactive group into the inert molecule which in turn, becomes the substrate for phase-II enzymes. Phase II reactions are usually detoxification in nature involving the interactions of the polar functional groups of phase I metabolites.They are conjugation reactions which conjugate the product of phase-I reactions with an endogenous substance such as sugar, sulphate, glutathione, etc. making the end product metabolite more hydrophilic and thus excretal.



Sites on drugs where conjugation reactions occur include carboxyl (-COOH), hydroxyl (-OH), amino (NH_2), and sulfhydryl (-SH) groups. Products of conjugation reactions are usually inactive unlike phase I reactions which often produce active metabolites.

Consequences of Drug Metabolism (Phase I and Phase II reactions):

Formation of-

- Inactive metabolite products.
- Metabolites similar to the parent drug.
- Metabolites more active than the parent drug.
- Metabolites with new pharmacological action.
- Toxic metabolites.

2. Phase I Reactions

The metabolic changes of drugs are due to Phase-I reactions which are catalysed by MFOS. Cytochrome P450(CYP)- a terminal oxidase, NADPH-CYP reductase and cytochrome b_5 are the important electron transport components of MFOS[14,15]. CYPs are the major enzymes involved in

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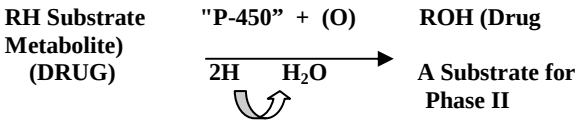
drug metabolism including bio-activation and use a variety of small and large molecules as substrates in enzymatic reactions [16].

Phase I reactions may occur by oxidation, reduction, hydrolysis, cyclization, and decyclization, addition of oxygen or removal of hydrogen. The most common reaction catalyzed by CYP is "monooxygenation", where one atom of oxygen (of O_2) is incorporated into an organic substrate (RH) whereas the other oxygen atom is reduced to water using an electron from NADPH[16].

$$\mathbf{RH + O_2 + 2H + 2e^- \rightarrow ROH + H_2O}$$



Oxidation is manifested as hydroxylation, epoxidation, dealkylation, and other transformations [17, 18]. The CYP, in addition to the hydroxylation reactions, also oxidize the hetero atoms including nitrogen and sulphur. The CYP-mediated oxidation of aliphatic double bonds or aromatic hydrocarbons leads to the formation of epoxides, which may either be labile intermediates or stable products. These epoxides can then be converted into dihydroxy metabolites known as "diols", by the hydrolysis reactions catalyzed by epoxide hydrolase (EH) [19, 20]. Phase I metabolism of drug candidates can be simulated in the laboratory using non-enzyme catalysts[4]. A bio mimetic reaction tends to give products that often contains the Phase I metabolites [21]. As an example, the major metabolite of the pharmaceutical trimebutine, desmethyltrimebutine (nor-trimebutine) can be efficiently produced by in vitro oxidation of the commercially available drug.

Table 1. Types of reactions catalysed by MFOS

Type of Reaction	Name of the Enzyme	Organ Site
Methylation	Methyltransferase	Liver, kidney, lung, CNS
Sulphation	Sulfotransferases	Liver, kidney, intestine
Acetylation	N-acetyltransferases,Bile acid-CoA: amino acid, N-acyltransferases	Liver, lung, spleen, gastric mucosa, RBCs, lymphocytes
Glucouronidation	UDP-glucuronosyltransferases	Liver, kidney, intestine, lung, skin, prostate, brain
Glutathione conjugation	Glutathione S-transferases	Liver, kidney

CYPs –Diversozymes

CYPs have been named on the basis of their cellular (cyto) location and spectrophotometric characteristics(chrome): When the reduced heme iron forms an adduct with CO, CYP enzymes absorb light at wavelengths near 450 nm, identifiable as a characteristic Soret peak. CYP was demonstrated to be a hemoprotein of the b-type class consisting of iron in its +3 oxidation state. The Fe^{3+} on reduction, is converted to Fe^{2+} that facilitates the binding of CYP with ligands such as O_2 and CO. [22-24]. Depending on the substrate and

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enzyme involved, CYP enzymes can catalyse a wide variety of reactions.

The "diversozyme"-CYP superfamily is a large and diverse group of enzymes carrying ou diversified functions [25]. Human CYPs are primarily membrane-associated proteins, located either in the inner membrane of mitochondria or in the endoplasmic reticulum of cells. Along with carrying out metabolism of drug xenobiotics, CYP enzymes are involved in the metabolism of endogenous substrates such as steroids, bile acids, fatty acids, eicosanoids, and fat soluble vitamins. Though CYPs metabolize thousands of endogenous and exogenous chemicals, some CYPs metabolize only one (or a very few) substrates, such as CYP19 (aromatase), while others may metabolize multiple substrates while other CYPs may act on one chemical or substrate [26].

These characteristics of CYPs account for their central importance in medicine and CYPs have received attention for drug development.

Genes encoding CYP enzymes, and the enzymes themselves, are designated with the abbreviation CYP, followed by an Arabic numeral indicating the gene family, a capital letter indicating the subfamily, and another numeral for the individual gene. The convention is to italicise the name when referring to the gene. For example, *CYP2E1* is the gene that encodes the enzyme CYP2E1 – one of the enzymes involved in paracetamol (acetaminophen) metabolism.
CYPs are categorized based upon their amino acid sequence similarities and are grouped in families, which are made up of subfamilies. Some members of CYP1, CYP2 and CYP3 are involved in drug and steroid metabolism. Others such as CYP11, CYP17, CYP19 and CYP21 are involved only steroid synthesis. CYP39, CYP46 and CYP51 are involved in cholesterol synthesis, CYP7 is involved in bile acid biosynthesis and CYP24 is involved in vitamin D degradation. CYP5 is associated with thromboxane A2 synthase; while CYP26 with retinoic acid hydroxylase. CYP4 catalyses arachidonic acid or fatty acid metabolism [27 -34]. CYP 3A4 plays pivotal role in drug metabolism [35].

Bioactivation-Metabolic Activation

Though most of the drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body, many substances are bio-activated by CYPs to form their active compounds [11]. Various examples existing with the inert carcinogenic agents, referred to as "procarcinogens", are metabolized into proximate or ultimate carcinogens by the CYP system (bio-activation). Benzo(a)pyrene (B(a)P), a ubiquitous pollutant, is an excellent example of this type of reaction[36- 38].

A common Phase I oxidation which involves conversion of a C-H bond to a C-OH bond, sometimes converts a pharmacologically inactive compound (a prodrug) to a pharmacologically active one. Phase I metabolism converts acetonitrile to $HOCH_2CN$, which rapidly dissociates into formaldehyde and hydrogen cyanide, both of which are toxic. Thus Phase I reactions can turn a nontoxic molecule into a poisonous one. Sometimes the drug metabolites, in addition to the parent drugs, can themselves exert adverse effects.

Some drugs may have two or three metabolites with different activities and thus have different implications. The analgesic action of acetanilide is exerted mainly through N-acetyl p-aminophenol, the major metabolite of the drug which is excreted in a

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conjugated form [39- 41]. A minor fraction of the drug deacetylates to form aniline having an adverse physiological effect on haemoglobin.

3. Factors Affecting Drug Metabolism

The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized to inactive products. The factors enhancing the rate of metabolism (induction) of a pharmacologically active metabolite will result in the reduction of the duration and intensity of the drug action and may lead to treatment failure. The inhibition may cause opposite effects leading to increase in the plasma concentrations of the drug and augmenting the effect of the drug action by increasing efficacy or toxicity of the drug. However, in cases where an enzyme is responsible for metabolizing a pro-drug into a drug, enzyme induction can speed up this conversion and increase drug levels, potentially causing toxicity. Various physiological and pathological factors can affect drug metabolism[42,43]. Physiological factors that can influence drug metabolism include age, individual variation (e.g., pharmacogenetics), enterohepatic circulation, nutrition or sex differences[12].
Genetic variation (polymorphism) accounts for some of the variability in the effect of drugs and polymorphic drug metabolism may have toxicological implication [44-47]. With Nacetyltransferases (involved in Phase II reactions), individual variation creates a group of people, who acetylate slowly (slow acetylators) and those who acetylate quickly, This variation may have dramatic consequences, as the slow acetylators are more prone to dose-dependent toxicity. CYP enzymes can also vary across individuals, with deficiencies occurring in 1 - 30% of people, depending on their ethnic background.

Pathological factors such as liver, kidney, and heart diseases can also influence drug metabolism. In patients with kidney disease, drugs have to be administered with dose adjustment for reduced renal function. This is particularly so in the case of drugs with narrow therapeutic windows and may translate into clinically significant variations in exposure and response[48].

The environmental factors and smoking also affects drug metabolism [49-51]. MFOS components are inducible by certain drugs such as bar-biturates, antidepressants, rifampicin. This may influence metabolism of other drugs such as that of diazepam metabolism [53-56]. In silico modelling and simulation methods allow drug metabolism to be predicted in virtual patient populations prior to performing clinical studies in human subjects[56]. This can be used to identify individuals most at risk from adverse reaction.

Drug Interactions

The consequences of defective metabolic activities, inhibitions and induction of drug metabolising system have implications in pharmacological activity of the drugs[37, 57-59].

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme or by directly inhibiting the activity of the CYP. This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with significant side-effects and drugs with small therapeutic windows. An anti-epileptic drug Phenytoin, for example, induces CYP1A2,

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CYP2C9, CYP2C19, and CYP3A4. Substrates for the later may be drugs with critical dosage such as amiodarone or carbamazepine. Blood plasma concentration of may either increase due to enzyme inhibition in the former, or decrease because of enzyme induction in the later. Since drug such as trimetrexate is metabolized by a CYP enzyme system, drugs that induce or inhibit this drug metabolizing enzyme system may elicit important drug-drug interactions that may alter drug -trimetrexate plasma concentrations. The agents that might be co administered with trimetrexate in AIDS patients for other indications that could elicit this activity include erythromycin, rifabutin, ketoconazole, and fluconazole. Cimetidine was found to cause a significant reduction in trimetrexate metabolism and acetaminophen altered the relative concentration of trimetrexate metabolites possibly by competing for sulphate metabolites. The nitrogen substituted imidazole (ImD) drugs (clotrimazole, ketoconazole, miconazole) were potent, non-competitive inhibitors of trimetrexate metabolism. It has been suggested that the patients medicated with these drugs and trimetrexate be carefully monitored [58, 60, 61].

Interactions with Naturally Occurring Substances

Not only can the xenobiotics act as inhibitors or inducers of MFOS[62, 63], but naturally occurring compounds also modify the hepatic drug metabolism, which can affect manifestation of drug action as well as the rate of metabolism of other chemicals[34, 57, and 64]. The bioactive compounds(bergamottin, dihydroxybergamottin, and paradisin-A), present in grapefruit juice inhibited CYP3A4-mediated metabolism of certain medications, leading to increased bioavailability[65]. In this case there is a strong likelihood of overdosing. Saint-John's wort, a common herbal remedy induces CYP3A4, and also inhibits CYP1A1, CYP1B1, CYP2D6, and CYP3A4 [66]. Tobacco smoking induces CYP1A2 which catalyses metabolism of clozapine, olanzapine, and fluvoxamine). At relatively high concentrations, starfruit juice has also been shown to inhibit CYP2A6 and other CYPs[67] .Watercress is also a known inhibitor of CYP2E1, which may result in altered drug metabolism for individuals on certain medications such as chlorzoxazone[68].

Tannic acid (TA), a hepatotoxin, occurs in a variety of natural food stuffs, fruits and drinks such as tea, coffee, cocoa, etc. inhibits MFOS activities *in vitro*[69,70]. When Phenobarbital (PB), a hypnotic and a broad spectrum inducer of MFOS, was given prior to TA; it restored the TA-depressed levels of drug metabolizing enzymes. When rats were treated with PB and TA, the altered 'nett' *in vitro* drug metabolism was summation of the effect of each agent .Many compounds which modulate endoplasmic reticulum and drug metabolism exert 'biphasic' effects [71, 72]. The hepatotoxic compounds are affected mainly in the first phase i.e. inhibitory action causing disintegration of endoplasmic reticulum, as reported in the case of TA. Inducers like PB and pentobarbital have a strong action on the second phase linked with induction. TA also potentiated the sleeping time of the barbiturates which could have been due to an acute interaction of TA with the components of MFOS, resulting in to less effective metabolism of drug substrates such as barbiturates which are present simultaneously[72-74]. Inhibition of CYP enzymes by naturally occurring substance like TA is of concern as it can also interfere with essential

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physiological processes involving CYP. Modulation in CYP can lead to changes in severity of toxic lesions produced by certain xenobiotic substrates of CYP and also can result into unwanted prolonged pharmacological action of the drug substrates. This can lead to changes in duration of pharmacological actions of certain drugs[4, 9, 57, 75-77]. Thioacetamide(originally used as a fungicide, a potent hepatotoxin), caused alterations in components of MFOS, with a decrease in hepatic drug metabolising enzyme levels. Both thioacetamide and its metabolite thioacetamide sulfine were converted by these enzymes to hepatotoxic compounds [78,79].

Many hepatotoxins increased microsomal lipid peroxidation which is known to compete with MFO for the reduced equivalents[80]. The rates of lipid peroxide formation were significantly induced due to TA ingestion. The increase may be related to the damage and disorientation of endoplasmic reticulum by endogenous-TA[81, 82]. Microsomal CYP enzymes can be inhibited by the generalised destruction associated with microsomal lipid peroxides[83-85]. PB, when given alone or prior to the treatment of thioacetamide increased in vitro metabolism of aminopyrine and decreased lipid peroxidations[78].

Influence of Diet On Drug Metabolizing System

Various dietary factors have marked effects on the metabolism of drugs, environmental chemicals and certain endogenous substrates[86]. TA bio-activation is primarily mediated by hepatic CYP2E, a major constitutive enzyme of mammalian liver with critical roles in xenobiotic metabolism and is induced by certain patho-physiological states such as starvation, diabetes, and obesity[87,88]. Hepatic CYP2E1 expression is also notably influenced by nutritional factors. Mechanism-based liver injury of TA is also highly augmented in diabetic condition [88,89].

Earlier studies on rats liver have indicated that the activities of various hepatic drug metabolizing enzymes are influenced by various dietary ingredients, e.g. protein, fat and vitamins [90-92]. Reports from different laboratories have indicated the need of different dietary constituents for maintaining the normal level of hepatic drug metabolizing enzyme activities [93,94]. The activities of drug metabolizing enzymes such as aminopyrine/ethylmorphine/N-methylaniline demethylases and aniline hydroxylase were decreased in low protein fed animals. A marked reversal in activities of drug metabolizing enzymes were noted when chronic deficient animals were re-fed in a controlled diet. The animals malnourished by the long term ingestion of a low protein diet have decreased capacity for drug enzyme activities [91,95]. The decrease in microsomal electron transport components during protein and riboflavin deficiencies has been noticed. Complete protection was observed in the presence of alpha-tocopherol in animals fed the low protein diet [96].

The dietary fats play an important role in determining the levels of several hepatic CYP mediated drug metabolizing enzymes [97]. The role of the polyunsaturated fatty acid composition of the endoplasmic reticulum in the regulation of the rate of oxidative drug and carcinogen metabolism is well established [98]. Studies related to the role of dietary lipids in regulating the activities and amounts of EH, UDP-glucuronosyl transferase and glutathione S-

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transferase in rat liver indicated that dietary lipids co-induce MFO enzymes in rat liver[99]. The activities of drug metabolising enzymes may have certain selective fatty acid phospholipids requirements that are modified by both quality and quantity of fatty acids present in the diet [100,101]. A source of dietary essential fatty acids is also required for the induction of MFO enzymes by the classic inducer-PB [102,103].

The MFO activities including B(a)P hydroxylase, which reflects metabolism of pro carcinogen B(a)P, is increased on exposure to various chemicals and drugs[104]. The type of inducer and of dietary fat along with the quantity of dietary fat are important regulatory factors in controlling induction of B(a)P hydroxylation and thus in modulating toxicity of B(a)P and other polycyclic aromatic hydrocarbons and drugs and thus in chemical carcinogenesis[100, 102, 105, 106]. The inclusion of unsaturated fat such as 20% corn oil (rich on n-6 fatty acids) or 20% menhaden oil(rich in n-3 fatty acids) in diet did not result in any significant induction of B(a)P hydroxylase activity during PB treatment. However feeding the rats with 20% coconut oil (rich in saturated fatty acids) resulted into a significant induction of the enzyme activity[105,106].

Alteration of the activating step(s) during metabolism of chemical carcinogens plays a significant role in the enhancement effect of fat on chemical carcinogenesis[107]. Potential for dietary fats to qualitatively or quantitatively alter the ratio of these activating and detoxifying systems may be extremely important in understanding the role of diet in the initial step(s) in drug detoxification or carcinogen activation[108].

4. Imidazole Drugs And MFOS

Many pharmacologically active compounds including widely used drugs contain imidazole (ImD) ring .Inhibitory and induction capacities of imidazole in drug metabolism may have profound clinical and toxicological significance [109]. Number of drug interactions involving the inhibition of hepatic microsomal drug metabolism by imidazole drugs has been reported[110, 111].

The cytotoxic epoxides and arene oxides are formed as intermediary products during oxidation of xenobiotics including drugs. The mono functional epoxides are acted upon by the microsomal EH a detoxifying enzyme and are converted into toxic diols. EH catalyses the hydrolysis of cis epoxides to trans dihydrodiols. Certain pharmacologically active ImD derivatives while acting as inhibitors of CYP monooxygenase enhance EH activity and thus can affect the metabolism of drugs that are metabolized via epoxide diol pathway directing their metabolic fate. The alterations of microsomal EH activity by ImD derivatives could be important in determining the overall metabolic fate of drugs. The antifungal ImD drugs such as ketoconazole and clotrimazole have been shown to stimulate rat liver microsomal EH. EH activity with non - sterically hindered cis epoxide substrates is enhanced in vitro by ImD imidazole derivatives with lipophilic substituent[112] and the activation was shown to be in an uncompetitive fashion(nonessential activation)[113]. Further, the ImDs stimulated the hydrolysis of only smaller substrates [114]. The studies define at least in part, which type of the substrates that would be susceptible for the in vitro stimulation by ImDs. The ImDs can be used as chemo- preventive agents who may act by increasing the rate of hydrolysis of small monofunctional cytotoxic epoxides, without affecting or decreasing the hydrolysis of

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complex large epoxides like BP 4, 5 oxides. The different factors such as phospholipid content, substrate structure and size are important in determining the overall metabolic fate and toxicity of compound metabolized via epoxide-diol pathway and are important in deciding the enhancement of EH by ImD drugs[114,115]. Ketoconazole may affect pharmacological action of co-administered drug and the toxicity of environmental pollutants entering in biosystem, as its effect on drug metabolising system found to be selective [116].

Clotrimazole, a widely used drug for the management of a variety of superficial dermatophyte infections of the skin was shown to inhibit the activities of the microsomal CYP involved in B(a)P metabolism and is a potent inhibitor of CYP-dependent transformation of poly-cyclic aromatic hydrocarbons[117]. Clotrimazole decreased hexobarbital sleep-times which were correlated with induction of CYP[118]. The dominant effect of ImD derivatives on B(a)P metabolism varies with rat pre-treatment and EH activity limits the rate of formation of B(a)P 9,10-dihydrodiol by the inducer-3-methylcholantrene, but not by PB treatment[119]. When administered in vivo miconazole nitrate (ImD-containing anti-fungal drug) stimulated EH activity, but had a substrate-dependent biphasic effect on CYP-dependent monooxygenase activities. The results suggested that a metabolite of miconazole was responsible for the inhibition [72].

ImD Drugs and Skin CYPs

Skin is the largest organ of the body that is exposed to a variety of substances either purposefully (drugs) or accidentally (environmental pollutants). Skin MFOS contributes substantially to overall xenobiotics metabolism and thus drug metabolism in particular. [120,121]. Therefore, a understanding of the mechanisms of drug metabolising enzyme system in the skin is important. Several studies have shown significant induction of drug metabolising enzyme activities and CYP content in skin by the topical or systemic administration of a wide range of xenobiotics. The topically applied drugs may undergo a degradation or activation process, which may result in skin sensitization or even carcinogenesis [122,123]. Several CYP inhibitors such as synthetic flavones and plant phenols reduce the amount of carcinogenic compounds in skin by inhibiting the MFO aryl hydrocarbon hydrolase activity which in turn, decreases the binding of carcinogens to DNA [124].

Because of the critical role of CYP in the biochemistry of fungi and protozoa, these enzymes may serve as targets for drug development for certain types of skin disorder. Several CYP inhibitors including some anti-fungal agents have successfully been used in therapy against skin disorders. The fungicidal properties of drugs depend on their ability to inhibit the synthesis of ergosterol, a major constituent of the fungal cell membrane, and block CYP-dependent demethylation of lanosterol. Ketoconazole binds to CYP enzymes and inhibits cells from producing ergosterol, the main component of the cell wall [125].

An insight into the mechanism of action of various cutaneous CYP is helpful in the development of novel therapy against skin disorders. Many studies have implicated the existence of multiple CYPs such as CYP2B12, CYP2C13, CYP2D1, CYP2D4, CYP2E1, CYP3A1, and CYP3A2 in the skin[126]. CYP1A1 was found to catalyse metabolism of various polycyclic aromatic

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hydrocarbon[127]. In addition to carrying out metabolism of various xenobiotics, skin CYP enzymes act on many endogenous substrates including vitamin D and vitamin A, which are widely used in clinical practice for treating a variety of dermatological disorders. Thus the mammalian CYP also play important roles in the biosynthesis of skin endobiotics which are shown to have implications in the development of certain skin disorders like psoriasis and atopic eczema [128]. Some skin diseases, such as psoriasis, are associated with increase in levels of several CYP[129]. In view of the involvement of CYP in leukotrienes and retinoic acid (RA) metabolism, some ImDs has been shown to possess anti-psoriatic action[130]. Skin CYP26A1, CYP26B1 and CYP26C1 are capable of metabolizing RA which is widely used for treating a variety of skin diseases][131-133]. Liarozole, which is an ImD-containing compound, is known to inhibit the CYP mediated metabolism resulting in an increase of RA levels in skin and plasma [134]. Biological function of vitamin D is also dependent on specific CYP enzymes.Vitamin D and its analogs possess a potential for novel drug development for skin diseases. Ketoconazole inhibited 1,25D-induced epidermal CYP24 activity [135, 136].

Therapeutic potential of ketoconazole, clotrimazole, and liarozole against a number of dermatological lesions, including cancer is being reported [117, 137, and 138]. Both liarozole and ketoconazole, as well as certain other azoles have shown great promise for several dermatological conditions. Several azole-based inhibitors of CYP have been shown to be useful for a variety of dermatological conditions. In psoriatic plaque, two CYPs namely CYP2S1 and CYP2E1 were enhanced, implying a differential adaptive response to oxidant exposure in lesional psoriatic skin. CYP4A11 may participate in the defence mechanism against UV-induced oxidative damage [139]. Thus CYP research is an integral part of drug development for skin diseases and skin-care products as well.

The CYP have a very vast range of substrates, including health and beauty-care products, industrial pollutants, anaesthetics, solvents, dyes, and plant products (such as flavones and odorants), to which the human skin is either intentionally or un-intentionally exposed. The mechanism of action and regulation of CYP is important for devising novel strategies for the management of a variety of cutaneous disorders.

The efficacy of therapeutic agents, which is dependent on skin metabolism, may be modulated by CYP and therefore a search for novel CYPs, their substrates in the skin and understanding the mechanism of their action is required. This may be helpful in designing newer approaches for the management of skin disorders.

5. Emerging Concepts

An application of pharmacogenetics and pharmacogenomics to clinical practice will change the way drugs are selected. Gene polymorphisms are the basis of this inter-individual response to drug therapy and they determine individual absorption, disposition, metabolism, and excretion of drugs. They also determine the sensitivity of drug target sites, such as receptors. The best-characterized pharmacogenetic polymorphisms are those of the CYP family. The identification of susceptible genes for common diseases with polygenic inheritance patterns may also provide information on genetic polymorphisms resulting in variation in drug response [129]. In the recent review on the vital role played by CYP, an

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inclusion of patients cohorts genotyped for the common CYP polymorphism and assessment of potential pharmacogenetic variability in drug clearance was recommended [42].

The bioconversions using CYP enzymes have emerged as a powerful alternative.CYP enzymes can provide an effective option for selective oxidation of unactivated CH bonds in drug synthesis, as synthetic chemistry lacks general catalysts for such a reaction[140,141]. Naproxen and ibuprofen, the two widely administered drugs are substrates of CYP 2C9 which is one of three main hepatic human CYPs invivo. It has been reported that CYP BM3 variants from Bacillus megaterium (counterparts of human CYP 2C9) act on diverse substrates including drugs such as Naproxen and ibuprofen. These variants can also act on desmethylnaproxen, the human metabolite of naproxen [140].

CYPs are also responsible for biosynthesis of the anti-cancer drug paclitaxel and the anti-malaria drug artemisinin[142,143]. Furthermore, they can also serve as sensors or bioremediation agents [144]. Thus CYPs have wide-ranging applications in the production of drugs and drug metabolites or as catalysts in other chemical processes. In recent times, the research on the applications of CYP in drug development is focused on protein engineering [145]. Engineered CYPs are being used in metabolic pathways to produce valuable pharmaceuticals such as benzyl hydroxy pyrolidine[146]. A variety of CYP BM3 has been engineered to hydroxylated and/or dealkylated many bioactive compounds including resveratrol, phenacetin, ethoxyresorufin, lovastatin, and simvastin. Almost all the human metabolites of the drugs verapamil and astemizole have been generated by CYP BM3 mutants. These mutants can be examined for hydroxylation and demethylation of bioactive compound classes including cyclopentenones, ibuprofen, Coreylactones, and 5 phenyloxazoline derivatives [147]. A structure-guided chimeragenesis can be used to create a CYP with collective beneficial merits of parent CYPs from bacteria and insect [148]. A transgenic mice with a gene for various human CYP including CYP 2D6 involved in metabolism of basic compounds and ultimately in that of many cardiovascular, antihypertensive and CNS-acting drugs had been produced [149].

The herbal medicines are often co-administered with the therapeutic drugs and the photochemical in herbal medicines have interactions with pharmacological agents (herb-drug interactions) which include inhibition or induction of dug metabolizing enzyme system. Interactions between phytochemicals and CYP are well recognised because of their clinical and toxicological implications. The extracts of herbal medicines such as Phyllanthus amarus were shown to inhibit various human CYP particularly CYP 3A4 and phyllanthin and hypophyllanthin were found to be the potent mechanism-based inhibitors of CYP 3A4 [150].

CYPs have received attention for drug development because of their diversified functions of metabolising wide variety of pharmaceutical agents. The relationship between dietary fat type and metabolism of drugs as well as carcinogens such as B(a)P , is important in deciding the pharmacological action of the drugs as well as the toxicity of the carcinogens. The understanding of the interactions of endogenous drug substrates of CYP and the antifungal imidazole drugs is imperative in drug development for skin diseases. Various aspects such as interactions of CYP with drugs , environmental pollutants and naturally

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occurring compounds including herbs; drug-drug interactions, reactive metabolite formation, type of diet and polymorphism, play role in modulating the rate of drug metabolizing enzymes, which ultimately determine the pharmacological action of the drug. An insight in to the mechanism of these interactions, the newer understanding of pharmacogenic polymorphism and the emerging applications of CYP will contribute to the development of safer and more efficient therapies.

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