# CHEPTER II

# LITERTURE REVIEWS

*Centella asiatica* (L.) Urban, a prostrate, perennial herbaceous creeper belongs to the genus of *Centella* L. in family Umbelliferae (Apiceae). This plant flourishes abundantly in moist areas and distributes widely in tropical and subtropical countries up to an altitude of 1800 m. This plant is clonally propagates producing stolons that are characterized by long internodes and nodes, on which are borne reniform-cordate leaves and sessile flowers in simple umbels (Figure 1). It is commonly known as Gotu kola in Chinese, Indian Pennywort in English, Brahmi in Hindi and Manduukaparani in Ayurveda. This plant is utilized as an important folk medicinal herb by natives of Asia, southern and middle Africa, southeastern United States and Australia, with a long history of therapeutic uses since ancient times (Zhang and Qin, 2007).
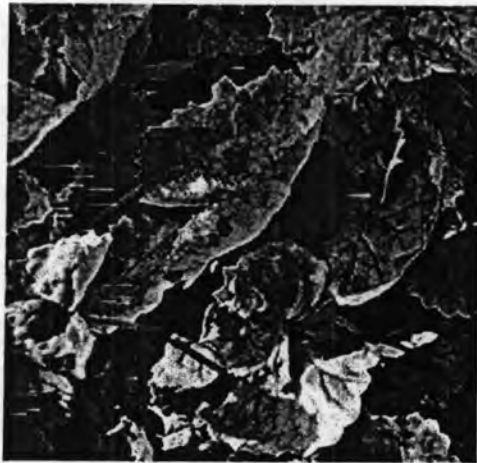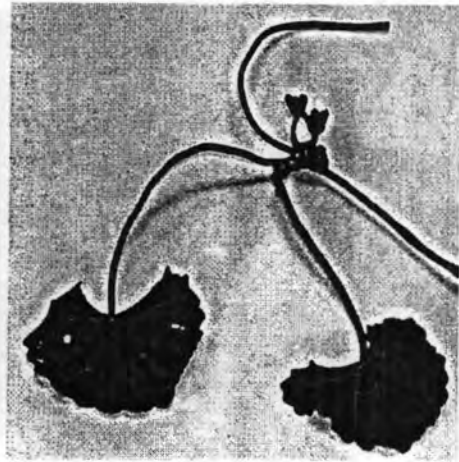


(A)                                              (B)

Figure 1 *Centella asiatica* leaves (A) and plant (B)

C. *asiatica* contains several active constituents, of which the most important are triterpenoid saponins, including asiaticoside, centelloside, madecassoside, and asiatic acid (Figure 2).In addition, *C. asiatica* contains other components, including volatile oils, flavonoids, tannins, phytosterols, amino acids, and sugars (Zhang and Qin, 2007).
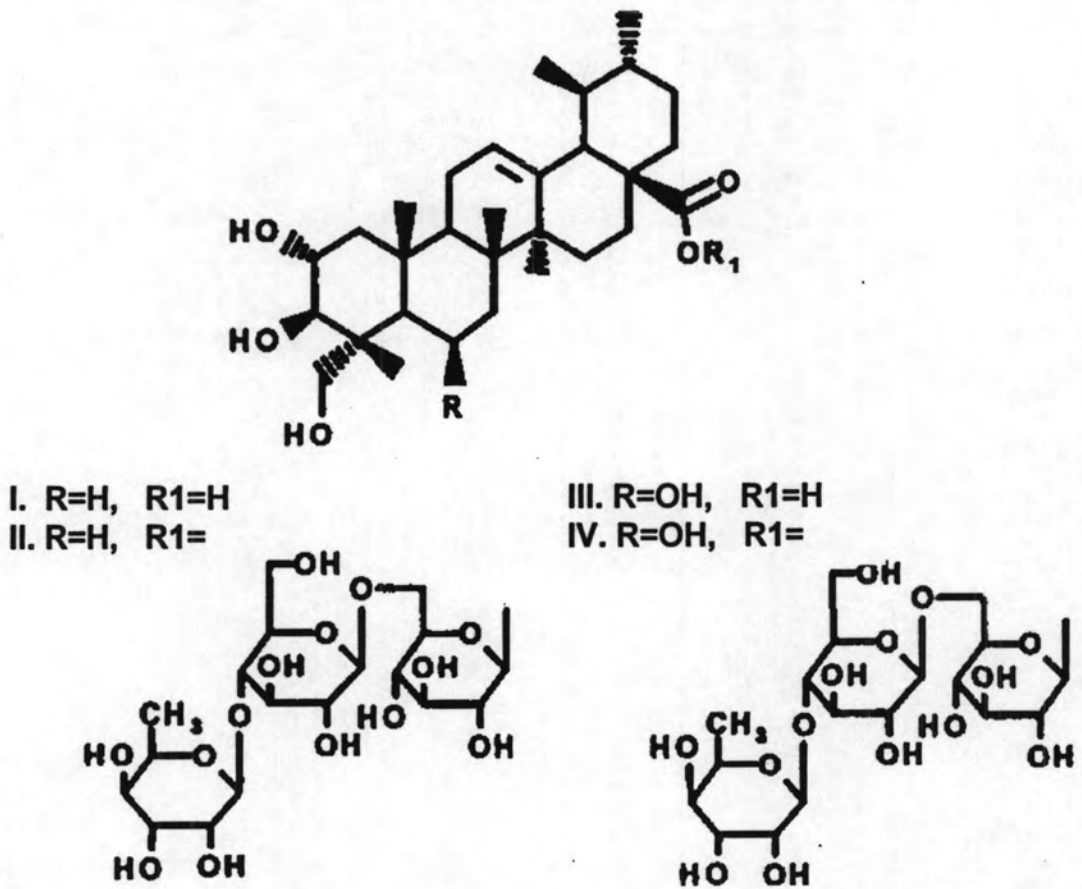


I. R=H, R1=H

II. R=H, R1=

III. R=OH, R1=H

IV. R=OH, R1=

Figure 2. Structures of asiatic acid (I), asiaticoside (II), madecassic acid (III) and madecassoside (IV) (Inamdar, 1996)

## Pharmacological effect

### 1. Wound healing effects

Activity of asiaticoside, isolated from *C. asiatica*, has been studied in normal as well as delayed-type wound healing conditions. In guinea pig, punch wounds were topically applied of 0.2% solution of asiaticoside twice daily for 7 day. It was shown to produce 56% increase in hydroxyproline, 57% increase in tensile strength, an increase of collagen content and better epithelisation. In streptozotocin diabetic rats topical application of 0.4% solution of asiaticoside over the punch wounds showed an increase of hydroxyproline content, tensile strength, collagen content and epithelisation there by facilitating the healing. Asiaticoside was also active by the oral route at 1 mg/kg dose in the guinea pig punch wound model. It promoted angiogenesis in the chick chorioallantoic membrane model at 40 μg/disk concentration (Shukla et al., 1999).

### 2. Brain stimulating effects

Oral administration of *C. asiatica* to mice at 200 mg/kg for 15 days was found to enhance the learning and memory as assessed by the radial arm maze test as well as enhance the cognitive function (Sulochana et al., 2005). Kumar and Gupta (2002) found that an aqueous extract of whole plant of *C. asiatica* improved learning and memory in normal rats given the extract at doses 100, 200 and 300 mg/kg for 14 days. It was shown to increase in number of avoidance in shuttle box and prolongation of step through latency in step through apparatus in a dose dependent manner.

Effect of pure asiaticoside extract from *C. asiatica* on anxiolytic effect was reported. For elevated plus maze model, there was a significant difference for number of closed arm entries and the time spent on the closed arm at the doses of 1 and 3 mg/kg. In addition, the number of unprotected head dips was significantly increased by the 3 mg/kg dosage. The open field test revealed that rats spent significantly more time at the center of the arena when treated with the asiaticoside at 3 mg/kg (Wijeweera et al., 2006). In additional, *C. asiatica*'s ethyl acetate fraction has additivity on some antiepileptic drug such as phenyltoin, valproate and gabapentin (Vattanajun et al., 2005)

## 3. Antioxidant effect

Cardioprotective effect of *C. asiatica* on myocardial marker enzymes and antioxidant enzymes in adriamycin induced cardiomyopathy was investigated in rats. Adriamycin (2.5 mg/kg, i.p) caused myocardial damage that was manifested by the elevation of serum marker (Lactate dehydrogenase, LDH; creatine phosphokinase, CPK; glutamate oxaloacetate transaminase, GOT and glutamate pyruvate tranaminase,GPT) enzymes. Both pre and co-treatment with the aqueous extract of whole plant of *C. asiatica* (200 mg/kg, orally) significantly prevented these alterations and restored the antioxidant enzymes (superoxidase dismutase, SOD; catalase, CAT; glutathione peroxidase; GPx and glutathione S-transferase; GST) activities to near normal levels (Gnanapragasam et al., 2004).

In addition to the antioxidant effect of the aqueous extract on rats, the effect of the aqueous extract of *C. asiatica* was evaluated on the course of kindling development, kindling-induced learning deficit and oxidative stress markers in pentylenetetrazole (PTZ) kindled rats. Rats were administered of *C. asiatica* (300 mg/kg, orally) one hour before injected PTZ (30 mg/kg, ip) on every second day until the development of the kindling. The result showed that administration of *C. asiatica* decreased the PTZ-kindled seizures and caused an improvement in the learning deficit induced by PTZ kindling as evidenced by decreased seizure score and increased latencies in passive avoidance behavior (Gupta et al., 2003).

Aqueous extract of whole plant of *C. asiatica* possessed an antioxidant property in rats given doses of 200 and 300 mg/kg. There was showed a significant decrease in the brain levels of malondialdehyde (MDA), which is the end product of lipid peroxidation and there was a simultaneous significant increase in levels of glutathione, which is antioxidant enzymes in brain (Kumar and Gupta , 2002).

Subathra et al, (2005) reported that administration of *C. asiatica* (water/50% ethanol) extract to rats at the doses of 300 mg/kg for 60 days reduce a lipid peroxide, decreased level of protein carbonyl and enhanced the activities of SOD, CAT, GPx in aged rat (above 24-months).

## 4. Actions on gastric ulcer

Cheng and Koo, (2000) examined effect of *C. asiatica* on the prevention of ethanol induced gastric lesions in rats. Oral administration of *C. asiatica* at 0.05g/kg, 0.25g/kg and 0.50g/kg before ethanol administration significantly inhibited gastric

lesions formation (58% to 82%) and decreased mucosal myeloperoxidase (MPO) activity in a dose-dependent manner. These results suggested that *C. asiatica* prevented ethanol induced gastric mucosal lesions by strengthening the mucosal barrier and reducing the damaging effects of free radicals.

The water extract of *C. asiatica* and its major component, asiaticoside, accelerated the healing of gastric kissing ulcers. They were found to promote angiogenesis, facilitate epithelial proliferation, and suppress MPO activity during ulcer healing stage. Similar effects were observed after 0.25 g/kg of *C. asiatica* or 10 mg/kg of asiaticoside administration. This was suggested that asiaticoside might be the most active ingredient in *C. asiatica* that enhanced ulcer healing (Cheng et al., 2004).

## 5. Immunological activities

S3A was a Rhamonogalacturonan I (RG-I) pectin isolated from *C. asiatica* that contained Rha, Ara, Gal, Glc and GalA in molar and had been found to have a backbone composed mainly of the disaccharide repeat unit. The pharmacological study showed that, S3A-N enhanced the proliferation of B-lymphocytes, S3A-L, S3A-I, S3A-S and S3AP3 had similar proliferate effects on both T- and B-lymphocytes (Wang et al., 2003).

A water-soluble acidic arabinogalactan name HBN was obtained from *C. asiatica*, contained Ara, Gal, Rha, GalA and Xyl in molar, had remarkable immuno enhancing activities on T- and B-lymphocyte, increased spleen index and inhibited the level of IgG and enhanced the secretion of IFN-g, IL-12 and IL-6, and inhibited IL-10. (Wang et al., 2005).

## 6. Anti-cancer activities

Antigenotoxic effect of acetone extract of *C. asiatica* against the genotoxic effect induced by cyproterone acetate (CPA), a synthetic progestin which is not only a genotoxic agent but also a tumor initiating agent, on human lymphocytes using chromosomal aberrations and sister chromatid exchanges as parameters. The result showed that *C. asiatica* extract at the concentrations of $1.075 \times 10^{-4}$, $2.125 \times 10^{-4}$, $3.15 \times 10^{-4}$ and $4.17 \times 10^{-4}$ g/ml of the culture medium was given along with two doses of CPA, 20 and 30 µM. It was shown that *C. asiatica* extract decreased the genotoxic damage caused by CPA in a dose dependent manner. The extract also caused

significant reduction in the frequency of cells with chromosomal damage and sister chromatid (Siddique et al., 2008)

Methanolic extract of *C. asiatica* showed 100% cytotoxicity at the concentration of 100 µg/ml and the concentration of *C. asiatica* required to produce 50% cell death was 62 µg/ml for Ehrlich ascites tumour cells (EAC) and 75 µg/ml for Dalton's lymphoma ascites tumors cells (DLA). Oral administration of the extract retarded the development of solid and ascites tumours and increased the life span of these tumour bearing mice. However, no toxic effects were detected in normal human lymphocytes (Babu et al., 1995).

In addition to the anti-cancer activity of *C. asiatica* in Caco-2 human colon cancer cells, anti-tumor activity of the crude water extract of *C. asiatica* using human colon adenocarcinoma-derived Caco-2 cells were examined. *C. asiatica* extract reduced the proliferation rate of Caco-2 cells significantly in a concentration-and time-dependent manner. The extract induced S and G2-M arrest in Caco-2 cells accompanied with apoptosis induction. The extract also increased the accumulation of cyclin B1 protein in the cells (Bunpo et al., 2005)

## 7. Toxicity

### Acute and chronic toxicity study

In 2003, Chivapat et al. investigated an acute and chronic toxicity of water extract of *C. asiatica* in Wistar rats. An acute toxicity, following orally administration of water extract of *C. asiatica* an observed for 14 day, the median lethal dose ($LD_{50}$) was found to be greater than 8 g/kg of body weight. A chronic study was performed by orally administration of extract at doses of 20, 200, 600 and 1200 mg/kg/day for 120 consecutive days. All doses of extract did not affect body weight and food consumption of rats. At the dose of 600 and 1200 mg/kg/day, *C. asiatica* caused significant decrease of white blood cell in male rats. In male rats at doses 600 mg/kg/day, the extract caused significant increase of these following clinical blood chemistry parameters: sodium, chloride. Likewise, the extract caused significant increase level of sodium in female rat at doses 1200 mg/kg/day.

## Clinical report

A case report of three women (61, 52, 49 years old) who developed jaundice after taking a tablet of *C. asiatica* extract for 30, 20, 60 days, respectively. The results of clinical laboratory tests were as following: alkaline phosphates (ALT): 1193, 1694 and 324 U/L; alanine aminotransferase (ALP): 503, 472 and 484 U/L; bilirubin: 4.23, 19.89 and 3.9 mg/dl. The liver biopsies of in-patient showed marked eosinophilic degeneration and cellular necrosis. Therefore, *C. asiatica* may be taken into account as a potential etiology of hepatic injury associated with apoptosis and necrosis (Jorge and Jorge, 2005).

# BIOTRANSFORMATION REACTIONS AND ENZYMES

Biotransformation is the conversion of lipophilic xenobiotics into more hydrophilic, water-soluble metabolites, thereby serving to reduce the biological half-life of the xenobiotics, change the biological activity of the xenobiotics and change the duration of the biological activity of the xenobiotics. Although other organs and tissues are also relevant, the liver is quantitatively the most important organ in the process of biotransformation, a process that may be divided into phase I and phase II.

## Phase I metabolism

Phase I metabolism includes oxidation, reduction, hydrolysis and hydration reactions as well as other rare miscellaneous reactions. The microsomal mixed-function oxides system (cytochrome P450-dependent) is importance reactions enzyme system in this phase. Mixed-function oxidase system found in microsomes (endoplasmic reticulum) of many cells (notably those of liver, kidney, lung and intestine) performs many different fuctionalization reactions. All of the above reactions require the presence of molecular oxygen and NADPH as well as the complete mixed-function oxidase system (cytochrome P450, NADPH-cytochrome P450 reductase and lipid). All reactions involve the initial insertion of a single oxygen atom into the drug molecule. A subsequent rearrangement and/or decomposition of this product may occur leading to the final products seen.

## Phase II metabolism

Phase II transformations are generally conjugative reactions of the parent xenobiotics or of phase I metabolites with, for example, inorganic sulfate, amino acids, glucuronic acid or glutathione. Conjugation reactions facilitate transport and enhance elimination via the renal and biliary routes.

## The cytochrome P450 superfamily of Enzymes

Cytochrome P450 (CYP) superfamily of enzymes is quantitatively and qualitatively important in the processing of xenobiotics. Largely the hepatic CYP enzymes process xenobiotics, which gain access to the general circulation either by parenteral administration or ingestion. CYP enzymes are mixed function monooxygenases capable of either inactivating or activating xenobiotics and endobiotics. The major elements of this system are phospholipid, a flavoprotein,

NADPH-cytochrome P450 oxidoreductase, and the hemoprotein cytochrome P450. Cytochromes P450 constitute the terminal binding protein of monooxygenase electron transport chains, and in addition to their prominent role in drug toxification/detoxification, they are also important for catalyzing the oxidation of endobiotics such as fatty acids, prostaglandins, steroids, ketones, and environmental chemicals such as polycyclic aromatic hydrocarbons, nitrosamines, hydrazines, and arylamines. CYPs have been characterized collectively as the most powerful *in vivo* oxidizing agents.

**Function**

The general reaction catalyzed by CYP enzymes is characteristic for mono-oxygenases and is shown in Figure 3. In most instances mammalian P450 enzymes catalyze reactions for the oxidative conversion of a chemical following the equation illustrated. Two electrons originating from NADPH are transferred to the hemeprotein by a flavoprotein (or a flavoprotein/iron sulfur protein) in the presence of organic chemical and molecular oxygen. The organic chemical is oxidized and one atom of molecular oxygen is incorporated into the chemical product.

P450-DEPENDENT OXYGENATION REACTIONS
$$NADPH + O_2 + AH_2 + H^+ \rightarrow NADP^+ + AHOH + H_2O$$

-----------------------------------------------------------------------

Microsomal P450 Reactions:

$$NADPH \rightarrow Flavoprotein\ (FAD\text{-}FMN) \rightarrow P450 \rightarrow O_2$$

cytochrome $b_5$

Mitochondrial P450 Reactions:
$$NADPH \rightarrow Flavoprotein\ (FAD) \rightarrow ISP \rightarrow P450 \rightarrow O_2$$

Figure 3. The equation for P450-dependent mixed-function oxidase (oxygenase) reactions and the two types of electron transport carrier systems functional with different P450s depending on their sub-cellular localization (Hasler, et al., 1999).

The P450s were categorized by families and sub-families based on the principle that a P450 protein sequence from one gene family is defined as usually having < 40% resemblance to that from any other family. Sub-families grouped

together proteins of <55% sequence similarity (shown Table 1). There are four main families of enzymes involved in the metabolism of drug (Table 2). More than 200 isozymes have been characterized from these families in terms of gene sequence.

Table 1. The human cytochrome P450 superfamily (Park et al., 1995).

| Family < 40% | Subfamily >55% | Protein enzymes |
|---|---|---|
| CYP1 | CYP1A | CYP1A1 |
| | | CYP1A2 |
| CYP2 | CYP2A | CYP2A6 |
| | | CYP2A7 |
| | CYP2B | CYP2B6 |
| | | CYP2B7 |
| | CYP2C | CYP2C8 |
| | | CYP2C9 |
| | | CYP2C18 |
| | | CYP2C19 |
| | CYP2D | CYP2D6 |
| | CYP2E | CYP2E1 |
| CYP3 | CYP3A | CYP3A3 |
| | | CYP3A4 |
| | | CYP3A5 |
| CYP4 | CYP4B | CYP4B1 |

Table 2. CYP Enzymes: Contribution to Drug Metabolism (Omari and Murry, 2007).

| Enzyme | Estimated contribution to drug metabolism (% of drugs metabolized by the enzyme) |
|---|---|
| CYP1A1/2 3 | 3 |
| CYP2A6 | 3 |
| CYP2B6 | 3 |
| CYP2C8/9 | 12 |
| CYP2C19 | 8 |
| CYP2D6 | 19 |
| CYP2E1 | 1 |
| CYP3A4/5 | 51 |

**Induction of cytochrome P450**

In view of the extremely broad substrate specificity of liver microsomal cytochrome P450 towards the metabolism of drugs, and the diversity of responses to inducers, it was initially proposed that these observations could be rationalized by assuming the existence of more than one form (or isoenzyme) of cytochrome P450. Thus different inducers would have the potential to elevate the levels of a specific sub-population of cytochrome P450, each with characteristic substrate specificity towards the metabolism of drugs. The induction of most CYPs occurs at the level of gene transcription, but CYP gene products are also stabilized under certain conditions, which also leads to increased hepatic CYP content. In rodents the classical CYP inducers phenobarbital up regulates CYPs from the 2B, 2C and 3A subfamilies. A receptor for phenobarbital has not been identified and the mechanism of induction remains a subject of continuing research. To some extent species differences in the potency of induction by phenobarbital and other inducers have complicated the issue, e.g., 1,4-bis[2- (3,5-dichloropyridyloxy)]-benzene induces murine CYPs 2B but is inactive in the rat. There are also species differences in some of the molecular processes of apparent importance in induction.

**Mechanisms of cytochrome P450 induction**

Although the precise molecular mechanisms of cytochrome P450 induction are not fully understood at present, much effort has been expanded in trying to rationalize the

inductive response of the drug-metabolizing enzymes in hepatic tissue. Figure 4. shows the functional components of the hepatic mixed function oxidase system responsible for cytochrome P450-dependent drug metabolism. Accordingly, induction of drug metabolism may arise as a consequence of increased synthesis, decreased degradation, activation of pre-existing components or a combination of these three processes. More specifically, Table 3 summaries some of the biochemical effects noted on response to enzyme inducers. From this table, it is clear that enzyme inducers have a variety of effects on the functional components of the mixed function oxidase system, particularly on the terminal haemoprotein. The common inducers of human cytochromes P450 are shown in Table 4.
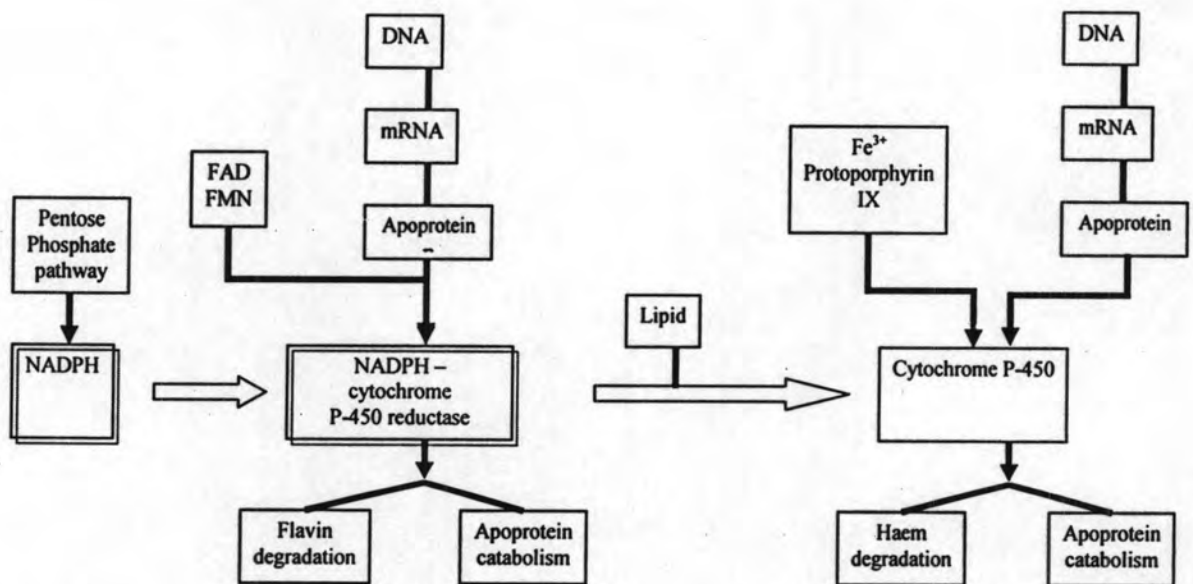


Figure 4. Synthesis and degradation of the functional components of the hepatic mixed function oxidase system (Gibsoon and Skette, 2001).

Table 3. Differences in induction mechanisms for cytochrome P450 (Gibson and Skette, 2001).

| P450 isoenzyme | Representative inducers | Main induction mechanism |
|---|---|---|
| 1A1 | Dioxin | Transcriptional activation by ligan activated Ah receptor |
| 1A2 | 3-Methylcholanthrene | mRNA stabilization |
| 2B1/2B2 | Phenobarbital | Transcriptional gene activation |
| 2E1 | Ethanol,acetone isoniazid | Protein stabilization (in part) |
| 3A1 | Dexamethasone | Transcriptional gene activation |
| 4A6 | Clofibrate | Transcriptional activation, mediated by peroxisome proliferator activated receptor |

Table 4. Common inducers of human cytochromes P450 (Erhardt, 1999).

| Cytochrome | 1A | 2C9 | 2E1 | 3A |
|---|---|---|---|---|
| Inducers | PAH (1A1/1A2) TCDD (1A1) β- naphthoflavone (1A2) omeprazole (1A2) | rifampin phenobarbital | ethanol isoniazid<br><br>acetone | rifampin phenobarbital<br><br>dexamethasone triacetyloleando mycin carbamazepine erythromycin terbinafine phenytoin lovastatin omeprazole |

### Inhibition of cytochrome P450

Enzymes inhibition decreases enzyme activity due to direct interaction with a drug (or other chemical). In a sense, this can be considered more serious than enzyme induction because inhibition happens rather immediately and does not take time to develop, in the manner that induction does. Further, there seem to be more reported incidences of drug-drug interaction problems that can be attributed to inhibition rater than induction. There are different types of enzyme inhibition, and the clinical effects are influenced by the basic mechanisms.

### CYP inhibition mechanisms: relationship to enzymic function

The determinants of CYP substrate specificity reside within the polypeptide chains, which are encoded by individual genes that are under distinct regulatory control. CYPs possess a ferroprotoporphyrin IX heme prosthetic group which activates oxygen for substrate metabolism. To appreciate the process of CYP inactivation by drugs, it is necessary to consider the CYP reaction cycle. Mechanisms of inhibition can device into two classes (Hasler et al, 1999).

#### 1. Reversible inhibition

Reversible inhibition occurs when a drug or metabolite attains concentrations near the CYP that are sufficient for impairment of enzyme activity. Diffusion of the inhibitor restores enzymic function so that inhibition is transient. Reversible inhibition of CYP enzymes, the most common type of inhibition, is due to the reversible interaction of a drug or a stable metabolite with a CYP enzyme. This process is probably responsible for most pharmacokinetic drug-drug interactions *in vivo*. Essentially, reversible processes would occur when a drug or stable metabolite inhibits an early step in the CYP reaction cycle, usually substrate binding or oxygen coordination to the heme. Thus, substrate turnover is decreased. Certain drug metabolites may be formed at rates that are sufficiently high to enable their accumulation within liver.

The sub-class of reversible inhibition is competitive, where the inhibitor and substrate compete for the same binding site on an enzyme. In the situations under consideration here, the inhibitor and the substrate would be drugs, competing for the binding site of a P450. This type of inhibition is easily identified by the classic intersecting plots seen *in vitro* studies.

The two situations are called noncompetitive inhibition, where the inhibitor binds at a site on the enzyme distinct from the substrate, and uncompetitive inhibition, where the inhibitor binds only to the enzyme substrate complex. Actually, neither of these have many clear examples in the literature of drug-drug interactions or in drug metabolism in general. An example of a noncompetitive inhibitor would be a reagent that modifies sulfhydryl groups remote from the substrate-binding site to attenuate the activity of an enzyme.

## 2. Irreversible inhibition

Irreversible inhibition occurs when the inhibitory agent is converted to a reactive metabolite that binds covalently to the CYP heme or apoprotein. Removal of this species is not usually possible and the loss of enzyme activity is permanent.

The term mechanism-based inhibition indicates that catalysis (at least one complete CYP reaction cycle) is required for the inhibition of enzyme activity. There are two basic types of mechanism-based processes that lead to irreversible enzyme inhibition: autocatalytic inactivation and metabolite intermediate (MI)-complexation.

Autocatalytic inactivation, or suicide processing, occurs when a reactive drug metabolite binds to CYP and alters its structure irreversibly, resulting in loss of function. Because only one or a few CYPs generate the reactive metabolite much greater selectivity of inhibition is observed than with reversible inhibitors. Inactivation is incomplete, there is usually partitioning between the formations metabolites and CYP destruction.

Metabolite-intermediate (MI) complexation of CYPs which occurs when drug metabolites are formed that bind tightly to the CYP heme .The distinction between autocatalytic inactivation and MI-complexation is that, in the latter, the hemeprotein is rendered catalytically inert but it is not destroyed. Some generalizations can be made about the arrangements of atoms in drugs that favour autocatalytic inactivation or MI-complexation of CYPs. (Hasler et al, 1999). The selective inhibitors of major CYPs are shown in Table 5.

Table 5.  The Selective inhibitors of the major CYP (Erhardt, 1999).

| CYP forms | Inhibitors | Mechanism |
|---|---|---|
| CYP1A2 | Fluroqunolones | reversible |
| CYP2C9 | Sulfaphenazole | reversible |
| CYP2D6 | Quinidine | reversible |
| CYP2E1 | disulfiram | irreversible |
| | Diethyldithiocarbamate (DDC) | irreversible |
| CYP3A | Troleandomycin (TAO) | Metabolite-intermediate |
| | gestodene | irreversible |
| | ethinylestradiol | irreversible |

An impact of CYP induction and CYP inhibition of xenobiotic on drug therapy, drug-drug interaction, adverse drug reaction and drug toxicity are mostly due to the modulation of CYP which is particular enzyme involving in the metabolism of the drug substrate. Currently used medicines which are substrate of individual isoform of CYP are shown in Table 6.

Table 6.  Drugs are metabolized by individual CYP isoforms (Coleman, 2005 and Tredger, & Stoll, 2002)

| CYP isoform | Substrate |
|---|---|
| 1A2 | Amitryptyline |
| | Imipramine |
| | Caffeine |
| | Fluvoxamine |
| | Clozapine |
| | Haloperidol |
| | Mexiletine |
| | Ondansetron |

Table 6. (con't) Drugs are metabolized by individual CYP isoforms (Coleman, 2005 and Tredger, & Stoll, 2002)

| CYP isoform | Substrate |
|---|---|
| 1A2 | Propranolol |
| | Theophylline |
| | Tracine |
| | Verapamil |
| | R-warfarin |
| | Zolmitriptan |
| 2B6 | Amfebutamone |
| | Coumarins |
| | Cyclophosphamide |
| | Mephenyltoin |
| | Methadone |
| 2E1 | Chlorzoxazone |
| | Ethanol |
| | Paracetamol |
| 3A | Astemizole |
| | Cannabinoids |
| | Cyclosporine |
| | Digoxin |
| | Erythromycin |
| | Felodipine |
| | Loratadine |
| | Nefazodone |
| | Meloxicam |
| | Methadone |
| | Ritonavir |
| | Sulfadimidine |
| | Tacrolimus |
| | Taxol |
| | Terfenadine |

Modulation of CYP is also contribute to increase or decrease human risks to environmental chemical toxicity, different CYPs isoforms have play a role in the bioactivation of different environment chemicals with carcinogenic potential. Table 7 shown a potential carcinogens and mutagens that are oxidized by various CYP isoform.

Table 7. The activation of potentially carcinogenic and mutagenic xenobiotics by select CYP isoforms (Coleman, 2005 and Erhardt, 1999)

| CYP isoform | Carcinogenic and and mutagenic xenobiotics |
|---|---|
| 1A1 | Polycyclic aromatic hydrocarbon (PAHs) such as naphthalene, Benzo[a] pyrene, 7,12-dimthybenz[a]anthracene (DMBA) |
| 1A2 | 2-amino-1-methyl-6-phenylimidzo[4,5-b] pyridine<br>2-amino-6-methyldipyrido[1,2-a:3,2'd] imidazole<br>2-amidopyrido[1,2-a:3,2'd] imidazole<br>2-amino-3-methylimidazo[4,5-f] quinoline<br>4-aminobiphenyl<br>2-naphthylamine<br>2-aminofluorene<br>2-acetylaminofluorene<br>2-aminoanthracene<br>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone<br>2-amino-3,5-dimethy-limidazo[4,5-f] quinoline |

Table 7 (con't) The activation of potentially carcinogenic and mutagenic xenobiotics by select CYP isoforms (Coleman, 2005 and Erhardt, 1999)

| | |
|---|---|
| 2E1 | Benzene |
| | Styrene |
| | Acrylonitrile |
| | Vinyl carbamate |
| | Vinyl chloride |
| | Ethyl carbamate |
| | Trichloroethylene |
| | Cabon tetrachloride |
| | Chloroform |
| | Methylene chloride |
| | N-nitrosodimethylamine |
| | N-nitrosodiethylamine |
| | 1,2-dichloropropane |
| | 4-(methylnitrosamino)-1-3-pyridyl)-1-butanone |
| 3A4 | aflatoxin B1 |
| | aflatoxin G1 |
| | sterigmatocystin |
| | 7,8-dehydroxy-7,8-dihydrobenzo(a) pyrene |
| | tris(2,3dibromopropyl) phosphate |
| | 6-aminochrysene |
| | senecionine |
| | 1-nitropyrene |