8 Extrahepatic Drug-Metabolizing Enzymes and Their Significance

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8.1	Summary	1
8.2	Introduction	2
8.3	Distribution and expression of DMEs in extrahepatic tissues	2
8.4	Factors influencing expression of extrahepatic DMEs	30
8.5	Role of extrahepatic DMEs in bioactivation and deactivation of xenobiotics	40
8.6	Significance of extrahepatic metabolism	42
8.7	Conclusions	63
	References	67

8.1 SUMMARY

Drug-metabolizing enzymes (DMEs) are primarily expressed in the liver but their role in the extrahepatic tissues such as gastrointestinal tract (GIT), pulmonary, excretory, nervous, cardiovascular system, and skin cannot be neglected. Generally, the expression of DMEs in extrahepatic tissues is quantitatively lower than that in the liver, but there are a few enzymes such as CYP1A1, CYP1B1, CYP2F1, and CYP2U1 that are more abundant in extrahepatic organs. As many extrahepatic organs are portals for administered drugs, DMEs expressed in these organs can be responsible for significant metabolism, leading to first-pass effects and lower bioavailability. Extrahepatic DMEs are also involved in bioactivation of prodrugs and formation of reactive metabolites that may interact with cellular components, resulting in organ-specific toxicity. Activity and expression of extrahepatic DMEs is often altered by coadministered drugs, leading to drug–drug interactions. Expression of DMEs in living beings affected by a host of

Encyclopedia of Drug Metabolism and Interactions, 6-Volume Set, First Edition.
Edited by Alexander V. Lyubimov.
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environmental and genetic factors such as genetic polymorphism, age, gender, pathophysiological conditions, inborn errors in metabolism, food habits, and environmental pollutants, contributing to varied drug effects and idiosyncratic toxicities.

8.2 INTRODUCTION

There was a stage when it was believed that DMEs in the liver were mainly responsible for the protection of the body against exogenous challenges (environment, diet, drugs, chemicals, etc.), while adrenal glands were involved in the metabolism of endogenous steroids. With time, DMEs have been found in extrahepatic organs and tissues including GIT, pulmonary, urinary, central nervous system (CNS), and cardiovascular system (CVS), as well as in skin, placenta, adrenal glands, reproductive organs, plasma, eyes, pancreas, and mammary glands. However, overall quantitative expression of extrahepatic DMEs represents just 10–20% of total hepatic metabolism. Nevertheless, some DMEs are found expressed solely in extrahepatic organs and tissues. Extensive studies have shown that extrahepatic enzymes play a significant role in drug metabolism and detoxification of environmental/food contaminants and provide protection to specific organs and the body as a whole.

A number of factors such as genetic makeup, age, gender, pathophysiological conditions, and environmental factors contribute to differential expression of DMEs in extrahepatic organs. The expression of DMEs, especially of cytochrome P450s (CYPs), is greatly influenced by both age and gender, and varies from fetal to geriatric age because of environmental factors as well as changes in levels of sex hormones. These DMEs contribute to bioactivation and deactivation of xenobiotics and to the development of diseases, especially cancer. The Human Genome Project has identified a correlation between extrahepatic CYPs and development of both solid and hematological malignancies.

DMEs in the GIT influence bioavailability of drugs significantly and drug clearance is dependent upon the rates of metabolism from hepatic and extrahepatic organs, in addition to the rate of excretion of the unchanged drug. These changes in turn affect the efficacy and safety of drugs by influencing their concentration and that of their metabolite(s) at the site(s) of action, which can result in severe drug–drug interactions in case of polypharmacy.

This chapter provides a comprehensive review of the type and nature of DMEs expressed in organs and tissues of the body, excluding liver. It also encompasses factors affecting the expression of extrahepatic DMEs, such as genetic polymorphism, age, gender, pathophysiological conditions, and food habits. Additionally discussed are observations on bioactivation and deactivation of xenobiotics, bioavailability and toxicity of drugs, and drug–drug interactions.

8.3 DISTRIBUTION AND EXPRESSION OF DMEs IN EXTRAHEPATIC TISSUES

Liver is quantitatively and qualitatively the most important site for metabolism of xenobiotics, including therapeutic drugs that enter the body after absorption from the GIT. A majority of the DMEs are expressed in the liver, although not evenly distributed

in the organ. DMEs such as CYPs are highly concentrated in the periportal region of the liver, while other enzymes such as glutathione *S*-transferases (GST) are expressed in the centrilobular of liver. This uneven distribution provides significant protection to this vital organ, for example, if toxic electrophilic intermediates are generated then only pericentral necrosis will occur, rather than massive necrosis [1].

DMEs similar to those expressed in the liver are also expressed in the extrahepatic organs. The distribution of DMEs in extrahepatic organs and tissues is depicted in Fig. 8.1 and detailed information, based on current literature, is described in Table 8.1. The expression of extrahepatic DMEs varies from organ to organ, depending on exposure to endogenous substances, routinely used drugs and the challenges faced because of food habits and the consequence of exposure to environmental contaminants [2–5]. There are some instances where DMEs show higher expression in extrahepatic tissues relative to the liver because of exposure to certain environmental components or because of life style choices (e.g., smoking or type of food intake).

8.3.1 CYPs and Subtypes

CYPs are monooxygenases and consist of an apoprotein and a heme moiety that is common to all isoforms. CYPs are involved in reactions that include hydroxylation, sulfoxidation, epoxidation, deamination, desulfuration, dehalogenation, peroxidation, *N*-oxide reduction, *N*-dealkylation, *O*-dealkylation, and *S*-dealkylation. CYPs constitute the largest family of DMEs localized in every organ of the body and are categorized based on amino acid sequence similarities. Among CYPs, CYP1, CYP2, and CYP3 are the major types responsible for the metabolism of xenobiotics [125]. The distribution of CYPs varies across the body. Pie charts depicting relative distribution of CYPs in different human organs are shown in Fig. 8.2 [126]. The total specific contents of CYPs in small intestine, lungs, kidneys, and brain have been observed to be 0.02–0.21 [127], ~0.01 [128], 0.1–0.2 [129], and ~0.1 nmol/mg [15], respectively.

8.3.1.1 Gastrointestinal Tract. Orally administered drugs first come in contact with CYPs located in epithelial cells of GIT. Major activity of CYPs at the cellular

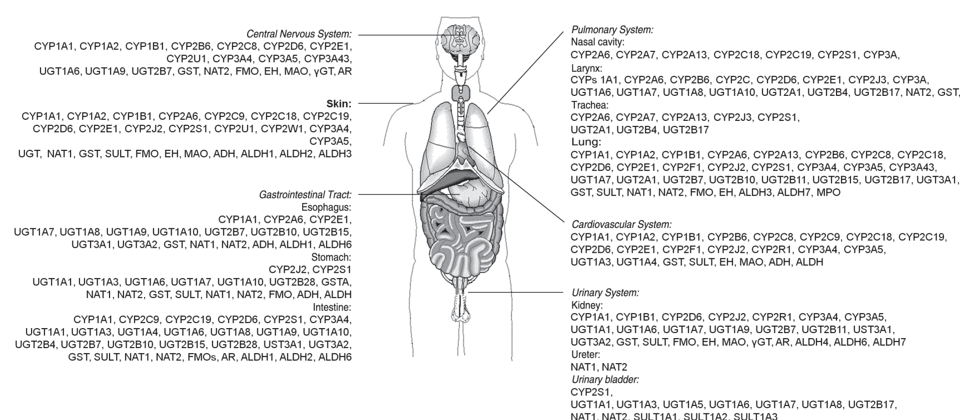

Figure 8.1 Distribution of drug-metabolizing enzymes in extrahepatic organs and tissues in humans.

TABLE 8.1 Location of Drug-Metabolizing Enzymes in Extrahepatic Organs and Tissues

Enzyme	Gastrointestinal Tract	Pulmonary System	Urinary System	Central Nervous System	CVS	Skin
CYP1A1	Enterocytes, esophagus 6	Bronchial epithelial cells, capillary endothelium, alveolar epithelium, alveolar type I and II cells, ciliated columnar epithelial cell lining, bronchoalveolar airways, alveolar macrophages 7	PCT 8	Cerebellum, cortex, basal ganglion, hippocampus, substantial nigra, pons, medulla oblongata 9,10	Left and right ventricles 11,12, coronary smooth muscle cells 13	Epidermis 14
CYP1A2	ND	Lung peripheral tissue 7	ND	Cerebellum, cortex, basal ganglion, hippocampus, substantial nigra, pons, medulla oblongata 15	Endothelium of endocardium, coronary vessels 16	Epidermis 17
CYP1B1	ND	Alveolar macrophage, bronchial epithelium 7	PCT 8	Putamen, spinal cord, medulla oblongata, frontal, temporal cortex 15	Heart 18, coronary smooth muscle cells 13	Epidermis 14
CYP2A6	Esophageal mucosa 19	Nasal mucosa, trachea, alveolar epithelium 7,20	NS	Striatum, thalamus, pons, medulla oblongata 21	Left ventricle 12	NS
CYP2A13	ND	Nasal mucosa, bronchial mucosa, alveolar epithelium 7,20	ND	Brain 20	—	NS

CYP2B6	ND	Clara cells, bronchial and peripheral tissue, epithelial cells, larynx, bronchial mucosa 7, bronchial epithelial cells 22	NS	NS	Endothelial cells 18	Foreskin epidermis, sebaceous glands, hair follicles 23
CYP2C8	Enterocytes 24	Serous cells of bronchial glands, bronchial tissue, peripheral tissue 7	NS	Cerebellum, cortex, basal ganglion 15	Right ventricle, left ventricle 11,12	NS
CYP2C9	Enterocytes 6	ND	NS	ND	Right ventricle, left ventricle 11,12	Epidermal keratinocytes 25
CYP2C18	Enterocytes 26	Trachea, serous cells of bronchial glands, bronchial tissue, peripheral tissue 7,27	NS	ND	Right ventricle 11	NS
CYP2C19	Enterocytes 6	Trachea 27	NS	ND	Right ventricle 11	Epidermal keratinocytes 25
CYP2D6	Detected at mRNA level but no activity reported 6,24	Bronchial mucosa 7	PCT 8	Putamen, globuspallidus substantial nigra 15	Right ventricle 11	Dermal fibroblasts 17
CYP2E1	Esophageal mucosa 19, colon mucosa 28	Nasopharynx, bronchial, bronchiolar epithelium, alveolar epithelium, endothelial cells 7	NS	Cerebellum, cortex, basal ganglion, hippocampus, substantial nigra, pons, medulla oblongata 15,29	Right ventricle 11, endothelium of endocardium, coronary vessels 16	Suprabasal cell layers of foreskin epidermis, keratinocytes 17

(*continued overleaf*)

TABLE 8.1 (*continued*)

Enzyme	Gastrointestinal Tract	Pulmonary System	Urinary System	Central Nervous System	CVS	Skin
CYP2F1	ND	Alveolar macrophages, epithelial cells, endothelial cells 7	ND	ND	Endocardium, coronary vessles 16, left ventricle 12, vascular endothelium 16	NS
CYP2J2	Epithelium lining of gastric pits, parietal cells of the gastric glands, intestinal smooth muscle cells 30	Bronchiolial and vascular smooth muscle cells, vascular endothelium, alveolar macrophages 7	PCT, CD, DCT 31	Autonomic ganglia cells 30	Heart 32	Keratinocytes 17
CYP2R1	NS	ND	Kidney 33	ND	Left ventricle 12,18	Keratinocytes 17
CYP2S1	Stomach, small intestine 33	Epithelial cells 7	Urinary bladder 34	White matter 34	ND	Cutaneous 35
CYP2U1	ND	ND	Kidney 36	Cerebellum 15,33	NS	NS
CYP3A4	Enterocytes 6, gastric parietal cells 37	Bronchial, bronchiolial and alveolar epithelium, alveolar endothelium, alveolar macrophages 7,38, nasal cavity, pharynx, larynx, trachea 39	CD 40	Cortex, basal ganglion 15	Endothelium of endocardium, coronary vessels 16	Keratinocytes 41

CYP3A5	ND	Bronchial, bronchiolial and alveolar epithelium, alveolar endothelium, alveolar macrophages 7,38, nasal cavity, pharynx, larynx, trachea 39	PCT 40	Midbrain, basal ganglion, frontal cortex 42	Endothelium, endocardium, coronary vessels, vascular endothelium 16	Keratinocytes 41
UGT	Complete GIT 43,44	Lung 43	Complete kidney 45,46	Brain 47	Heart 12	Stratum corneum 48
UGT1A1	Stomach, colon 43	NS	PCT, DCT 49, urinary bladder 50	NS	NS	NS
UGT1A3	Stomach, colon 43	NS	Urinary bladder 50	NS	Left ventricle 12	NS
UGT1A4	Colon 43	NS	NS	NS	Right ventricle 11	NS
UGT1A5	Complete GIT 50	NS	Kidney, urinary bladder 50	NS	NS	NS
UGT1A6	Stomach, colon 43	NS	PCT, DCT 49, urinary bladder 50	Brain 43	NS	NS
UGT1A7	Esophagus, stomach 43, small intestine, colon 50	Lung 51	PCT, DCT 49, urinary bladder 50	NS	NS	NS
UGT1A8	Esophagus, jejunum, ileum, colon 43	NS	Urinary bladder 50	NS	NS	NS

(*continued overleaf*)

TABLE 8.1 ***(continued)***

Enzyme	Gastrointestinal Tract	Pulmonary System	Urinary System	Central Nervous System	CVS	Skin
UGT1A9	Colon 43	NS	PCT, DCT 43,49	Brain 43	NS	NS
UGT1A10	Esophagus, stomach, intestine, colon 43	NS	NS	NS	NS	NS
UGT2A1	NS	Lung 7	NS	Brain 52	NS	NS
UGT2B7	Esophagus, intestine, colon 43	Lung 7	PCT, DCT 43,49	Brain 43	NS	NS
UGT2B10	Esophagus 43	Lung 7	NS	NS	NS	NS
UGT2B11	NS	Lung 43	PCT, DCT 43,49	NS	NS	NS
UGT2B15	Esophagus 43	Lung 7	NS	NS	NS	NS
UGT2B17	NS	Lung 7	Urinary bladder 50	NS	NS	NS
UGT3A1	Complete GIT 53	Lung 53	Kidney 53	ND	NS	NS
UGT3A2	Complete GIT 54	NS	Kidney 54	NS	NS	NS
NAT1	Esophagus, stomach, small intestine, colon 55	Bronchial epithelial cells, alveolar lining cells 7	Ureter, urinary bladder 55	NS	NS	Epidermal keratinocytes 56

NAT2	Esophagus, stomach, small intestine, colon 55	Bronchial epithelial cells, alveolar lining cells, laryngeal mucosa 7,55	Ureter, urinary bladder 55	Neural tube, hind brain 57	NS	ND
GST	Complete GIT 58	Lung 59	Kidney 60	Brain 61	Heart 62,63	Skin cytosol 64,65
GSTA	Duodenum, stomach, colon 58	Bronchial epithelium, bronchiolar epithelium 7	PCT, loop of henle, CD 66	NS	NS	Skin cytosol 64,65
GSTP	Duodenum, stomach, colon 58	Bronchial epithelium, bronchiolar epithelium 7	DCT, Bowmen's capsules, CD 31,67	Choroid plexus, vascular endothelium, ventricular lining cells, pia-arachnoid, astrocytes 61	NS	Skin cytosol 64,65
GSTM	NS	Lung 7	DCT, Bowmen's capsules, CD 31,67	Brain 61	NS	Skin cytosol 64,65
SULT	Duodenum, jejunum, ileum, stomach 68	Bronchial epithelial cells 7	CD medulla 31	Brain 69–72	NS	Skin 73,74
COMT	NS	NS	NS	Right inferior frontal gyrus, intraparietal sulcus 75	NS	NS

(*continued overleaf*)

TABLE 8.1 (*continued*)

Enzyme	Gastrointestinal Tract	Pulmonary System	Urinary System	Central Nervous System	CVS	Skin
γGT	NS	NS	Cortex 76	Brain 77	NS	NS
EH	NS	Bronchial epithelial cells 7	Cortex, medulla 78	Cerebral blood vessels, brain parenchyma 79	Heart 80	Epidermis, dermis, epithelial cells, fibroblasts 81–84
FMO1	Small intestine 85	Lung 85,86	Kidney 87	Magnocellular reticular nuclei, colliculi, substantia nigra 88	NS	Epidermis, dermis 89,90
FMO2	Small intestine 85	Lung 85,86,91	NS	Magnocellular reticular nuclei, colliculi, substantia nigra 88	Heart muscle 92	NS
FMO3	ND	Lung 85,86	Kidney 93	Magnocellular reticular nuclei, colliculi, substantia nigra 88	NS	Dermis 89
FMO4	Small intestine 85	Lung 85,86	Kidney 87	Magnocellular reticular nuclei, colliculi, substantia nigra 88	NS	Dermis, epidermis 94,95
FMO5	Small intestine 85	Lung 85,86	Kidney 96	Magnocellular reticular nuclei, colliculi, substantia nigra 88	Heart muscle 92	Dermis, epidermis 94,95
MAO	Small intestine 97	Lung 97	Kidney 98	Brain 99,100	Heart 97	Hair follicles, cutaneous nerve fibers beneath epidermis 101, fibroblasts 102–104

MAO-A	Small intestine 97	Lung 97	Cortex, medulla 98	Catecholaminergic neurons (cells of the substantia nigra, locus coeruleus, periventricular regions of hypothalamus) 99,100	Heart 97	NS
MAO-B	Small intestine 97	Lung 97	Cortex, medulla 98	Serotonergic neurons (dorsal raphe nucleus), astrocytes, posterior hypothalamic regions 99,100	NS	NS
β-Gluc	Brush border epithelium, microflora 105	Alveolar macrophages 106	NS	NS	NS	ND
ADH	Intestine 107	Lung 107	Kidney 107	Brain 108	Heart 109	Epidermis, sebaceous glands and hair follicles 110
ADH Class I	NS	NS	NS	Neurons of cerebral cortex, hypothalamus, infundibular stalk of the pituitary, purkinje cells of the brain cerebellum 108,111,112	NS	NS

(*continued overleaf*)

TABLE 8.1 ***(continued)***

Enzyme	Gastrointestinal Tract	Pulmonary System	Urinary System	Central Nervous System	CVS	Skin
ADH Class II	Esophagus, stomach 112	NS	NS	NS	NS	NS
ADH Class III	Whole body 112	Whole body 112	Kidney 112	Whole brain 112,113	NS	NS
ADH Class IV	Stomach 112	NS	NS	NS	NS	NS
ADH Class V	Stomach 112	NS	Fetal kidney 112	NS	NS	NS
ALDH	Esophagus, stomach, intestine 114	Lung 114	Kidney 115	Brain 116	Heart 109	Skin 117
ALDH1	Esophagus, stomach 118	Lung 119	ND	NS	NS	Epidermis, dermal appendages 117

ALDH2	Esophagus, stomach 118	ND	ND	NS	NS	Epidermis, hair follicles 120
ALDH3	ND	Lung 115	ND	NS	NS	Epidermis, dermal appendages 117
ALDH4	ND	ND	Kidney 115	NS	NS	NS
ALDH5	ND	ND	ND	NS	NS	NS
ALDH6	Esophagus, stomach 118	ND	Kidney 115	NS	NS	NS
ALDH7	ND	Lung 115	Kidney 115	NS	NS	NS
AR	Intestine 121	NS	Papilla of epithelial cells, endothelial cells, interstial cells, CD 122	Brain 123	NS	NS
MPO	NS	Lung 124	NS	NS	NS	NS

Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AR, aldose reductase; β-Gluc, β-glucuronidase; CD, collecting duct; COMT, catechol-*O*-methyltransferase; CT, carboxyltransferase; DCT, distal convoluted tubule; EH, epoxide hydrolase; FMO, flavin-containing monooxygenase; GST, glutathione *S*-transferase; γ-GT, γ-glutamyltransferase; MAO, monoamine oxidase; MPO, myeloperoxidase; NAT, *N*-acetyltransferase; ND, not detected; NS, not specified; PCT, proximal convoluted tubule; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase; TPMT, thiopurine *S*-methyltransferase.

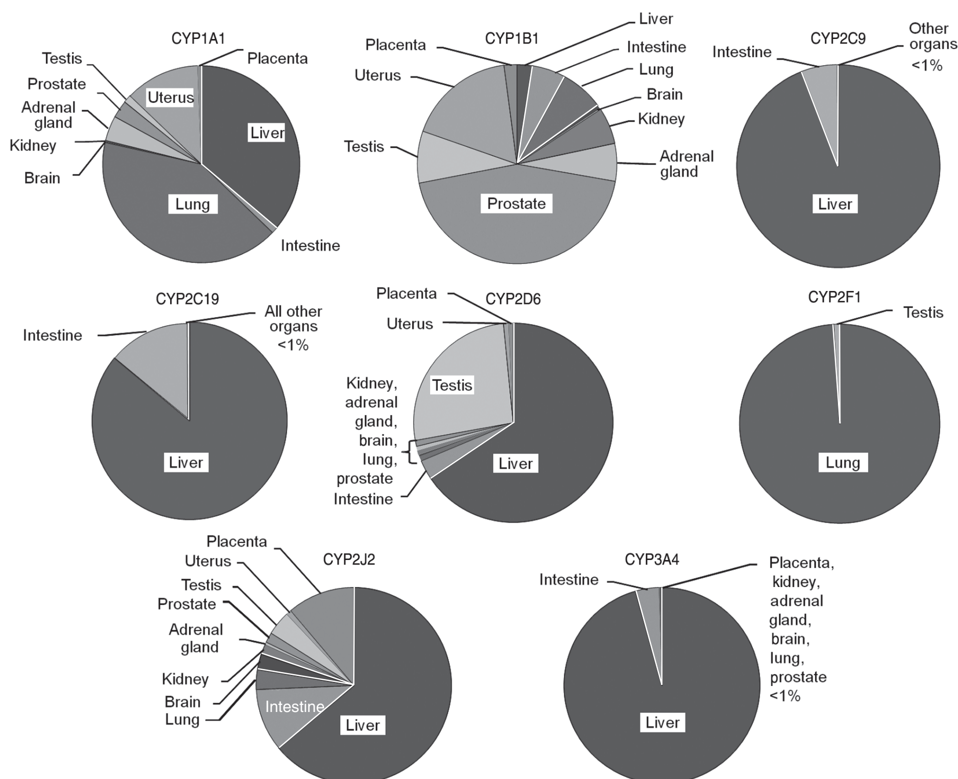

Figure 8.2 Percentage of expression of CYP mRNA in different organs. *Source*: The figure is based on data from Nishimura *et al*. [126].

level is in the villous tips and decreases in the direction of crypts. At the tissue level, CYP activity gradually decreases from the duodenum to the colon [127]. CYP1A1, CYP2C9, CYP2C19, CYP2D6, CYP2J2, CYP3A4, and CYP3A5 are the primary enzymes expressed in the GIT. In addition, CYP1A2, CYP2A6, CYP2A13, CYP2E1, CYP2F1, CYP2B6, and CYP2S1 are expressed at lower levels. Recently, mRNAs for CYP2S1, CYP2R1, CYP2U1, and CYP2W1 have been reported in the GIT but their contribution to the drug metabolism is not yet known [33,127].

The specific content of CYP1A1 in the small intestine varies from 3.6 to 7.7 pmol/mg of protein [127]. CYP1A1 expression is regulated by aryl hydrocarbon receptor (AhR) [130]. The ligands for the receptor are aromatic hydrocarbons, which are toxic to the body [131]. Zhang *et al*. correlated the expression of AhR with CYP1A1 along the length of the intestine from duodenum to ileum and found expression diminished markedly along the oral direction of intestine [130,132]. The extent of induction of CYP1A1 expression and activity could be related to the challenges faced, for example, exposure to polyaromatic hydrocarbons (PAHs) [24]. This enzyme can be induced in GIT by smoking, omeprazole, β-naphthoflavone (BNF), 3-methylcholanthrene, isosafrole, cyclohexanol, albendazole, phenobarbital, imazalil (food contaminant), benzo(α) pyrene, green tea extract and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) [133–139]. Although like CYP1A1, CYP1B1 is also regulated by AhR, no expression of this enzyme has been detected in the intestine [24].

Expression of CYP2B1/2 is reported to be 137 pmol/mg microsomal protein in the upper villi and it is not detected in the crypt cells of the human intestine except in the induced state, for example, by phenobarbital and imazalil [135,140]. CYP2B6 mRNA has also been reported in the human intestine, although its activity is not established [141].

CYP2C9 constitutes 15% of the total CYP content, with an average specific content of ~8 pmol/mg, as compared to 89 pmol/mg microsomal protein in the human liver [142]. The presence of this enzyme in the intestine is responsible for poor bioavailability of fluvastatin [127]. CYP2C19 constitutes 2% of the total CYP content in the human intestine, with a specific content of 2 pmol/mg microsomal protein [142]. mRNA expression of CYP2C isoforms in the human intestine is in the order of CYP2C9 = CYP2C18 > CYP2C19 > CYP2C8, while protein expression is in the order of CYP2C9 > CYP2C19 > CYP2C8 (below limit of quantification) > CYP2C18 (not detected) [143]. In human jejunum, both CYP2C9 and CYP2C19 exhibit polymorphisms [26] with a 19-fold interindividual variation in CYP2C19 activity [143].

The expression of CYP2D6 in the human intestine is reported to be 0.9 pmol/mg microsomal protein, which is ~14 times lower than the liver. Its concentration decreases in the order of jejunum > duodenum > ileum [144]. Although CYP2D6 shows 100-fold interindividual content variation in the intestine, while clinically, its contribution to first-pass metabolism is not significant [144]. CYP2E1 mRNA is detected in the intestine, but its activity has not been established [127]. CYP2J2 (arachidonic acid epoxygenase) constitutes about 1.4% of the total human intestinal CYPs [142], with a specific content of 2.1 ± 0.6 pmol/mg protein [145]. Its protein expression is relatively constant across the GIT [30]. CYP2J2 contributes to the first-pass metabolism of nonsedative antihistamines, astemizole, and ebastine [145]. CYP2S1 is highly expressed in epithelial cells of the GIT, with its expression being higher in the basal cell layer of the stratified squamous epithelium of esophagus. In stomach, CYP2S1 is located in the mucus secreting epithelial cells of the glandular mucosa covering the fundus and body. Its expression in the duodenum is strong in the columnar epithelial lining of the villi, in crypts, as well as in the cells surrounding the glands in the lamina propria. It is also located in the glandular epithelium of both colon and rectum [34].

CYP3A is the major enzyme expressed in the gut and constitutes up to 82% of the total CYPs [142]. CYP3A4 expression is highest in the small intestine and lowest in the stomach [146]. The specific content of CYP3A4 protein in human duodenum, distal jejunum, and distal ileum is in the range of 3–90, 2–98, and 2–38 pmol/mg, respectively [147]. CYP3A4 expression is regulated by the pregnane X nuclear receptor (PXR) [148] and induced by drugs such as rifampicin [149], phenobarbital [150], sodium arsenite [151], nafcillin, and dicloxacillin [152]. Intestinal CYP3A can also be inhibited by drugs including maslinic acid, corosolic acid, ursolic acid [153], ketoconazole [154], and imazalil [155]. CYP3A inhibitors and inducers affect the bioavailability of orally administered CYP3A substrates.

8.3.1.2 Pulmonary System. DMEs in the pulmonary system are responsible for the metabolism of drugs and also of environmental pollutants such as organic solvents and PAHs that are present in inhaled air [156]. Despite relatively low expression, these enzymes provide protection to the brain from inhaled chemicals and are important for homeostasis and metabolism of odorant molecules [157]. Apart from inhaled xenobiotics, drugs given by parenteral routes have the potential to accumulate in the lungs

as 100% of the cardiac output reaches the pulmonary system before passing through the liver and undergoes metabolism. Examples include amiodarone, imipramine, lidocaine, propranolol, pethidine, amphetamine, chlorphentermine, chlorpromazine, local anesthetics, and fentanyl [158–160].

The CYPs expressed in the pulmonary system are CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C18, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2S1, CYP3A4, CYP3A5, CYP3A43, and so on [7,156]. Of these CYP1A1, CYP1B1, CYP2A13, CYP2E1, CYP2F1, CYP2S1, and CYP3A5 are abundantly expressed in the pulmonary system at concentrations higher than that in the liver [7].

CYP1A1 is inductively expressed in bronchial epithelial cells, capillary endothelium, and alveolar epithelium of the human lungs in response to inhaled chemicals such as TCDD, BNF, pyridine, acetone, benzo(α)pyrene (cigarette smoke constituent), 3-methylcholanthrene, TCDD, nicotine, omeprazole, 2-hydroxypyridine, 7,12-dimethylbenz(α)anthracene, and diesel exhaust [7,161–166]. Its presence in the epithelium of bronchi is restricted to airways with a diameter greater than 1 mm [7]. A study to estimate the influence of smoking on the expression of CYP1A1 revealed that specific content of this isoform in nonsmokers was 6.0 pmol/mg in comparison to ∼15.5 and 19.0 pmol/mg in smokers and ex-smokers, respectively [167]. In contrast to CYP1A1, CYP1A2 is expressed constitutively [132], although inhaled benzo(α) pyrene and diesel exhaust can lead to its induction [166].

CYP1B1 is expressed in alveolar type I and II, ciliated columnar epithelial, alveolar macrophage epithelial, and bronchial epithelial cells of the human lungs [7,167]. It is responsible for 2- and 4-hydroxylation of 17-estradiol and metabolic activation of PAHs and aromatic amines, similar to CYP1A1 [166]. CYP1B1 has five-fold higher expression in the smokers' lungs [167]. Its expression is reported to be 1.8, 1.0, and 4.4 pmol/mg microsomal protein in smokers, nonsmokers, and ex-smokers, respectively [167].

In the human lungs, CYP2A6 and CYP2A7 are present in the trachea and alveolar epithelium, respectively [7]. CYP2A6 is prominently expressed in the liver and also found in the pulmonary system with mRNA expression of 9 ± 1, 76, and 160 ± 140 amol/mg RNA in lungs, trachea, and nasal mucosa, respectively [20]. CYP2A7 is virtually quiescent or absent in the human nasal mucosa and lungs [168]. CYP2A13 is present in pulmonary epithelial cells and the bronchial mucosa, with highest expression in the nasal mucosa, while hepatic expression is below the limit of quantitation [7]. mRNA expression in the lungs, trachea, and nasal mucosa is 78 ± 32, 130, and 750 ± 210 amol/mg RNA, respectively. The specific content of CYP2A13 in microsomes is in the range of 0.26–0.56 nmol/mg proteins [20]. It is associated with metabolism of 2′-methoxyacetophenone, 2,6-dichlorobenzonitrile, hexamethylphosphoramide (HMPA), *N*,*N*-dimethylaniline, *N*-nitrosodiethylamine (NDEA), *N*-nitrosomethylphenylamine, aflatoxin B, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NKK) [7]. CYP2B6/7 isoforms are located in bronchial epithelial cells and alveolar type II pneumocytes. CYP2B6 is associated with oxidation of NKK in the human lungs and bioactivation of the prodrug, cyclophosphamide [7].

CYP2C8 and CYP2C18 are predominantly expressed in serous cells of bronchial glands, bronchial mucosa, and peripheral tissues of the human lungs, while CYP2C9 shows very low expression in the bronchial mucosa [7,27]. CYP2C8 is believed to have a role in regulation of the pulmonary vascular and bronchial tone [159]. This

subfamily is involved in metabolic activation of drugs as well as carcinogens [27]. CYP2C18 has more abundance in the trachea, as compared to CYP2C19, which is predominant in the human lungs [27].

Guidice *et al*. [169] examined gene expression of CYP2D6 in the human bronchial mucosa and lung parenchyma and reported that the mean levels of CYP2D6 mRNA in the bronchial mucosa and lung parenchyma were three- and six-folds, respectively, lower than the liver and that the gene was nonuniformly distributed within the lung. CYP2E1 is present in the bronchial, bronchiolar and alveolar epithelium, endothelial cells, and the nasopharynx, and reported to metabolize tobacco-specific nitrosamines, such as *N*-nitrosodimethylamine (NDMA), *N*-nitrosodibutylamine, and *N*-nitrosodiethylamine [159,170]. CYP2E1 expression is significantly higher in lung adenocarcinomas and is induced by acetone and ethanol [162]. CYP2F1 is specifically expressed in the human lungs with no or minimal expression in hepatic and other organs [171]. It is responsible for the metabolism of environmental toxicants, such as components of cigarette smoke, gasoline, and industrial by-products such as benzene, styrene, naphthalene, and 3-methylindole [172,173].

The CYP2J subfamily is expressed in bronchial and vascular smooth muscle cells as well as endothelium. The enzymes are involved in epoxidation of arachidonic acid (AA), leading to epoxide AA metabolite, which modulates bronchial smooth muscle tone and airway transepithelial ion transport [7,159,174]. CYP2J2 and CYP2J3 subtypes are primarily expressed in ciliated epithelial cells lining of the airway [174]. CYP2S1 is expressed in the upper and lower respiratory systems, in particular, in the nasal mucosal epithelium of the upper respiratory tract, and at high levels in the epithelium of bronchus and cuboidal and columnar epithelia of bronchioles in the lung. The enzyme is induced by TCDD and smoking [34,175].

CYP3A is expressed in bronchial epithelium, bronchial glands, alveolar epithelium, vascular epithelium, capillary epithelium, and alveolar macrophages of the human lungs. It is also expressed in the nasal cavity, pharynx, larynx, and trachea [39]. CYP3A4 and CYP3A5 are expressed at a significant level in human lungs, whereas CYP3A7 and CYP3A43 have low expression [39,176]. CYP3A4 is located in epithelium cells of bronchial glands, bronchiolar ciliated and terminal cuboidal, epithelial cells, and type II alveolar epithelial cells [176]. CYP3A5 is present in bronchial and alveolar epithelial cells, bronchial glands, and alveolar macrophages [39]. Its levels are decreased in alveolar macrophages on cigarette smoking [177].

8.3.1.3 Urinary System. CYPs expressed in the human kidneys are CYP1A1, CYP2D6, CYP2E1, CYP2J2, CYP2R1, CYP3A4, CYP3A5, and so on [8,129]. These enzymes are present throughout the kidney, with highest concentrations in the microsomal fraction of the cortex and proximal convoluted tubule (PCT). The specific content of CYP1A1 is <0.005 pmol/mg proteins in each kidney [8]. CYP2E1 is located in the PCT and is induced by pyridine, ethanol, acetone, and pyrazole [129]. It is responsible for nephrotoxicity, as it generates reactive metabolites of chloroform, ipomeanol, 1,1-dichloroethene, and paracetamol [129]. CYP2J2 plays an important role in carcinogenesis and is located in PCT, collecting duct (CD), and distal convoluted tubule (DCT) cells, while it is absent in glomerulus and thin loop of Henle [31]. CYP2S1 is highly expressed in urothelial cell of the urinary bladder and in PCT and DCT of the kidney [34]. CYP3A4 is predominantly expressed in PCT, along with CYP3A5 [129,178].

8.3.1.4 Central Nervous System. The CYPs in the brain are distributed unevenly in different cells and regions. For example, CYP content in mitochondrial fraction of the brain cells is nine times higher than that in the microsomal fraction [179]. CYPs play a diverse role in the brain, including metabolism of xenobiotics, aromatization of androgens to estrogens, formation of catechols, and metabolism of neurotransmitters [180]. Centrally acting drugs, such as analgesics, antidementia agents, beta-blockers, tricyclic antidepressants, antipsychotics, monoamine oxidase inhibitors, and vasodilators, are metabolized in the brain [15]. CYPs are also present in the microvessels and choroid plexus of the brain, which indicates that regulation of the penetration of xenobiotics in the brain compartment might be due to their metabolism in endothelial cells of the blood–brain barrier [180].

The CYPs expressed in the human brain include CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2D6, CYP2E1, CYP2U1, CYP3A4, CYP3A5, and CYP3A43 [15]. The subtypes, CYP1A1, CYP1A2, CYP2B6, CYP2D6, and CYP2E1, are expressed in the cortex, cerebellum, basal ganglia, hippocampus, substantia nigra, medulla oblongata, and pons. Of these, CYP1A1, CYP1A2, and CYP2E1 along with CYP2A6 are expressed in the mitochondria of the striatum, thalamus, pons, and medulla oblongata. CYP1A1 bioactivates PAHs that form adducts with DNA and thus it has the potential to induce carcinogenesis [15]. Interestingly, the structure of human brain CYP1A1 is different than that present in the liver [9]. The CYP2A6 isozyme is mainly responsible for the metabolism of nicotine to cotine through C-oxidation and also to *trans*-3′-hydroxycotine by 3′-hydroxylation [181,182]. Some studies have shown that its activity is inhibited by neurotransmitters and steroids, such as tryptamine, serotonin, dopamine, histamine, noradrenaline, adrenaline, estrogen, androgen, and corticosterone [183]. CYP1B1 is predominantly located in the putamen, spinal cord, medulla oblongata, frontal, and temporal cortex and to a lesser extent in cerebellum, hippocampus, thalamus, and amygdale. It is predominantly expressed in the nuclei of a majority of astrocytes and neurons in human brain cortex [15].

CYP2B6 is located in the caudate nucleus, putamen, hippocampus, cerebellum, brain stem, thalamus, and frontal cortex [15]. Induction of CYP2B6 isoform has been reported in monkeys after chronic treatment with phenobarbital [184]. CYP2B6 and CYP2C19 are the major enzymes responsible for metabolism of selegiline, a drug used in the treatment of Parkinson's disease [185,186]. The activity of CYP2B6 toward metabolism of nicotine is reported to be relatively higher than CYP2A6 [15].

CYP2C8 is located in the frontal cortex, putamen, and hippocampus of the brain [187]. Typical CYP2C8 substrates are tricyclic antidepressants, diazepam, and verapamil [15]. CYP2D6 is highly expressed in the cerebral cortex, purkinje and granule cell layers of cerebellum, reticular neurons of midbrain, and pyramidal neurons and its expression in brain fractions, viz putamen, globus pallidus, and substantia nigra, is higher in alcoholics than in nonalcoholics [188–190]. The isoform is involved in metabolism of neurotransmitters, tryptamine, and tyramine [15]. CYP2E1 plays a significant role in fetal alcohol syndrome, as it is induced by ethanol. Increased expression of this subtype was observed in human neuroblast cultured cells treated with nicotine [191]. CYP2S1 is expressed in the white matter of the brain [34]. CYP2U1 is specific to the cerebellum [15] and is involved in the metabolism of arachidonic acid, docosahexaenoic acid (DHA), and other long-chain fatty acids [36].

CYP3A is present in the cortex and basal ganglia where it metabolizes psychoactive drugs, such as codeine [192,193]. The subtypes CYP3A4 and CYP3A43 are expressed

in equal amounts in the brain. CYP3A43 is highly expressed in the brain as compared to the liver and is involved in metabolism of drugs such as alprazolam [194]. CYP3A5 mRNA is reported in the midbrain, basal ganglia, and frontal cortex [42].

8.3.1.5 Cardiovascular System. CYPs play a vital role in modulation of cardiac Ca^{+} current and cell contraction and in maintaining vascular tone by generating epoxides such as 5,6-epoxyeicosatrienoic acids (EETs), 8,9-EETs, 11,12-EETs, and 14,15-EETs from AA [195]. The CYPs expressed in the human heart are CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A7, CYP2C8, CYP2D6, CYP2E1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, and CYP3A4 [196,197]. Of these, CYP1B1 and CYP2J2 are prominently expressed, while CYP1A1, CYP1A2, CYP2B6, CYP2B7, and CYP2C9 are induced [198]. Cardiomyocytes are efficiently involved in metabolism and clearance of drugs from the heart [199].

Healthy human heart shows no expression of CYP1A2, while there is limited expression of CYP1A1 in the left ventricle. In diseased conditions, like dilated cardiomyopathy, CYP1A1 is also detected in the right ventricle, ascending aorta, pulmonary aorta, and right atrium of the heart. CYP1A1 and CYP1B1 are expressed in coronary artery smooth muscle cells and are involved in the conversion of estradiol to hydroxyestradiol, which has cardiovascular protective effects [13].

CYP2C8, CYP2C9, and CYP2J2 show epoxygenase activity in the heart. CYP2C8 and CYP2C9 are present in the right and left ventricle cardiomyocytes [11,12,199] and are induced during ischemic heart injury [198]. CYP2J2 is abundantly expressed in coronary artery endothelial cells, smooth muscle cells, and cardiac myocytes of the normal human heart [200]. Expression of CYP2J2 is aggrandized on exposure with cocaine [201]. CYP2D6 shows very low expression in heart and is involved in the metabolism of verapamil [198]. CYP2E1 is expressed in the endothelium of the endocardium and coronary vessels [16], while CYP2S1 is absent in the heart [34,202]. CYP3A4 is expressed in the endothelium of the endocardium and coronary vessels. The CYP3A4-NADPH-CYP reductase system is involved in formation of nitric oxide from isosorbide dinitrate [16].

8.3.1.6 Skin. CYPs are present in keratinocytes, monocytes, lymphocytes, and fibroblasts of the human skin. CYPs are relatively highly expressed in keratinocytes [203] and also found within the differentiated cells of hair follicles and sebaceous glands, as well as in epidermis [204]. The role of CYPs is to provide protection to exposed skin from ingredients in cosmetics, toiletries, and healthcare products, as well as from many allergens, environment toxicants, and carcinogens. CYP isoforms expressed in human skin are CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP2S1, CYP2U1, CYP2W1, CYP3A4, and CYP3A5. Among these, CYP2C9, CYP2C18, CYP2C19, CYP2W1, CYP3A4, and CYP4B1 are upregulated by cellular differentiation [17]. CYP1A1 and CYP1B1 are expressed in the differentiated keratinocytes [14] and CYP2U1 is expressed at highest levels in undifferentiated keratinocytes [17].

CYP1A1 is expressed inductively in the human skin and hair follicles [205] and can be induced by ultraviolet (UV) irradiation, PAHs, BNF, polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and coplanar polyhalogenated byphenyls [14,17,206]. It is involved in the metabolism of benzo(α)pyrene, 3-methylcholanthrene, and 7,12-dimethylbenz(α)anthracene in the skin [203]. CYP1A2 is expressed at mRNA

level in epidermis of the human skin [17]. CYP1B1 is also expressed in the hair follicles and plays a major role in the metabolism of PAHs (7,12-dimethylbenz(α)anthracene). It is induced in the skin on exposure to UV radiation, especially in keratinocytes, basal cell layer, and dermis [14,207].

CYP2A7 mRNA is detected in human skin fibroblasts, although no catalytic activity has been observed [208]. CYP2B6 is reported in foreskin epidermis, epidermis, sebaceous glands, and hair follicles of adult skin [23]. Weak CYP2C mRNA expression is shown in epidermal keratinocytes and dermal fibroblasts of the human skin. This subfamily may play a role in the pathogenesis of drug-induced skin allergy, as this group of enzymes is known to metabolically activate drugs, including phenytoin [209]. CYP2C9 and CYP2C19 are unregulated in epidermal keratinocytes during cellular differentiation, and CYP2C18 is present in the human skin [17,25]. CYP2D6 is detected in dermal fibroblasts, while CYP2E1 is present in the suprabasal cell layers of human foreskin epidermis and keratinocytes [17]. The latter is induced by ethanol, dexamethasone, and salicylic acid [210]. CYP2J, CYP2W, and CYP2R mRNA has been detected in human keratinocytes [17]. CYP2S1 is constitutively expressed in the human skin and can be induced on UV exposure or topical drug treatment. Other factors responsible for CYP2S1 expression in the cutaneous tissue are PUVA (psoralen + UV-A treatment for eczema, psoriasis, graft-versus-host disease, and vitiligo), coal tar, and all-*trans* retinoic acid [35].

CYP3A4 is not expressed constitutively in the proliferating human skin keratinocyte but is induced by dexamethasone. In contrast, CYP3A5 mRNA is expressed constitutively [41].

8.3.2 Non-CYP Enzymes

This category includes phase I (e.g., aldehyde oxidase) and phase II DMEs that are involved in metabolic reactions including oxidation, reduction, hydrolysis, hydration, and group transfer. Extrahepatic non-CYPs DMEs include transferases, hydrolases, oxidases, dehydrogenases, reductases, peroxidases, and glucuronidase. These enzymes convert drugs into active/reactive/inactive metabolites in extrahepatic tissues and are essential for clearance and pharmacological activity of xenobiotics and are also responsible for the drug-induced toxicity.

8.3.2.1 Transferases. Transferases catalyze the transfer of functional groups from a donor to an acceptor molecule. These enzymes play a crucial role in converting electrophilic metabolites produced by phase I enzymes (e.g., CYPs) into less or nontoxic products [211–214]. Metabolic reactions catalyzed by transferase enzymes are shown in Fig. 8.3.

8.3.2.1.1 UDP-Glucuronosyltransferases. UDP-glucuronosyltransferases (UGTs) are located in the endoplasmic reticulum of mammalian cells and detoxify xenobiotics (e.g., therapeutic drugs, carcinogens and environmental pollutants) as well as endogenous compounds (e.g., bilirubin, bile acids, thyroid hormones and steroid hormones) [50,215]. About 40–70% of clinically used drugs are subjected to glucuronidation, resulting in hydrophilic products with low pharmacologically activity [216]. In humans, families of UGTs reported are UGT1, UGT2, UGT3,

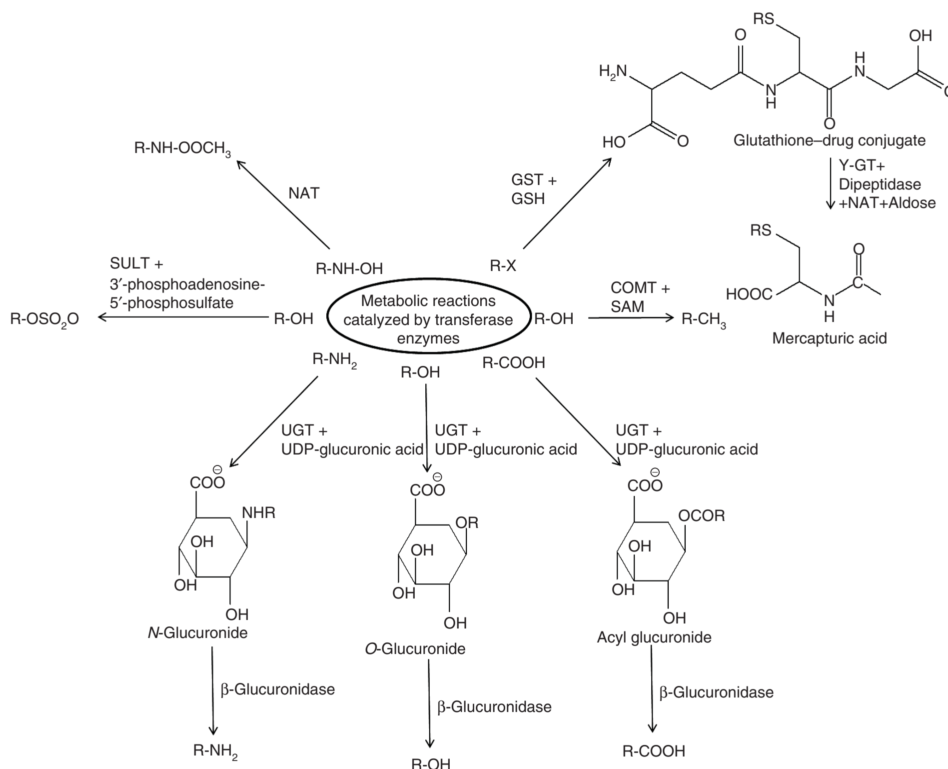

Figure 8.3 Metabolic reactions catalyzed by transferase enzymes.

and UGT8 [50,216]. UGT1A is involved in glucuronidation of NSAIDs, anticonvulsants, chemotherapeutics, steroid hormones, bile acids, and bilurubin. UGT2B isoforms, UGT2B7 and UGT2B15 metabolize endogenous substrates, including hydroxylated steroids and bile acids, and xenobiotics [50,217]. UGT3A1 uses UDP-*N*-acetylglucosamine as a substrate to glycosidate xenobiotics, while UGT3A2 uses both UDP-glucose and UDP-xylose to glycosidate a broad range of substrates, including 4-methylumbelliferone, 1-hydroxypyrene, bioflavones, and estrogens [54]. UGT3A1 contributes in the metabolism and elimination of ursodeoxycholic acid for ameliorating the symptoms of cholestasis or dissolving gallstones [53]. UGT3A2 has a more selective role in protecting organs from toxins [54]. UGT8 converts UDP-galactose to galactosidate ceramide, an important step in the biosynthesis of glycosphingolipids and cerebrosides [53,218]. These enzymes are distributed in the liver, GIT, lungs, kidneys, brain, placenta, reproductive organs, and so on [43,219]. The highest activity is reported in kidneys, followed by GIT and lungs [220].

The isoforms of UGTs expressed in human GIT are UGT1A1, UGT1A3, UGT1A4, UGTA5, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2A1, UGT2B4, UGT2B7, UGT2B10, UGT2B11, UGT2B15, and UGT2B28. UGT1A7 is prominently expressed in upper GIT, while UGT1A8 exists in the lower GIT [219]. The UGTs present in human esophagus are UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B10, and UGT2B15. In stomach, the isozymes reported are UGT1A7, UGT1A10,

and UGT2B28. The subtypes, UGT1A1, UGT1A3, and UGT1A6, exhibit polymorphisms in stomach. Most of the UGTs present in the duodenum exhibit polymorphism (viz UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT2B4, UGT2B7, and UGT2B15), except UGT1A10 and UGT2B28. In both jejunum and ileum, UGT1A10, UGT2B15, and UGT2B28 are the predominant DMEs, while UGT1A3 is additionally expressed in the jejunum. Expression of UGT isoforms UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B10, and UGT2B15 are highest in the colon [43,221,222].

Gregory *et al*. [219] reviewed literature and report that glucuronidation of bilirubin is catalyzed by UGT1A1 in the GIT and this isoform is involved in the conjugation of endogenous compounds (e.g., retinoic acid and estrogens) and xenobiotics. The isozymes, UGT1A5, UGT1A6, and UGT1A7, are involved in conjugation of xenobiotics, although their role in conjugating endogenous substrates is not yet established. The subtypes, UGT1A8, UGT1A9, and UGT1A10, are responsible for conjugation of mycophenolic acid and environmental pollutants such as PAHs. Tertiary amine drugs are conjugated by UGT1A4, oestrone by UGT1A3 and UGT1A10, while UGT2B4 and UGT2B7 are primarily involved in catalysis of hyodeoxycholic acid glucuronidation [223,224].

In human pulmonary system, the only UGT1A enzyme reported is UGT1A5 [43,225,226]. UGT1A6 and UGT1A8 are expressed in the larynx; UGT1A7 and UGT1A10 in the tongue, tonsils, floor of mouth, larynx, and esophagus; while UGT2B4 and UGT2B17 exhibit significant levels of expression through the aerodigestive tract [227]. UGT2A1 is prevalent in the aerodigestive tract, with highest expression in the lungs followed by trachea > tonsil > larynx > colon > olfactory tissue [43,225,226]. It provides protection against cancer by neutralizing tobacco carcinogens (PAHs, including 1-hydroxy benzo(α)pyrene, benzo(α)pyrene-7,8-diol, and 5-methylchrysene-1,2-diol) [226]. In other studies, UGT2B4, UGT2B11, and UGT2B17 have been shown to be present in the human bronchial epithelial cells [225,228].

The activity of UGT enzymes in the human kidneys is highest in PCT and DCT cells. For example, the propofol glucuronidation rate is higher in kidney than liver because of relative higher expression of UGT1A8 and UGT1A9 [43,45]. The human kidneys have low levels of UGT1A1 and UGT1A6 [49]. UGT1A9 and UGT2B7 are involved in the metabolism of endogenous and exogenous substances, which can result in renal drug–endobiotic interactions [229].

In the human brain, UGT1 is expressed in cerebellum and involved in glucuronidation of serotonin [230]. UGT1A6 is responsible for glucuronidation of propofol in the brain [231]; UGT2A1 is involved in glucuronidation of odorant compounds such as monoterpenoids, aliphatic alcohols, phenols, and coumarins and UGT2B7 metabolizes opioids and their metabolites (e.g., 3- and 6-hydroxyl morphine) [232,233]. UGT activity has been observed in the stratum corneum of the human skin [48].

8.3.2.1.2 N-Acetyltransferases. *N*-Acetyltransferases (NATs) are directly involved in *N*-acetylation of xenobiotics, such as aromatic and heterocyclic amines as well as drugs such as mesalamine (5-aminosalicylic acid, 5-ASA), isoniazid, sulfamethazine, and sulphasalazine [234–237]. Arylhydoxylamine metabolites generated by CYPs also undergo acetylation by NATs [234,235]. These enzymes have a role in the biotransformation of carcinogens and are inhibited by anticancer drugs, such as cisplatin and

tamoxifen [235]. NAT1 activity is increased in human cancer cells and can be induced by trichostatin A and inhibited by caffeic acid, ferulic acid, and gallic acid [238,239]. A well-known nonselective CYP inhibitor, 1-aminobenzotriazole, acts both as a substrate and an inhibitor of NAT1 [240]. The second human isoform, NAT2, is involved in *N*-acetylation of carbocyclic arylamines, such as 4-aminobiphenyl and β-naphthylamine [241]. Paracetamol, scopuletin, and curcumin [239,242] are reported to be inhibitors of NAT2.

NAT1 is widely distributed in the human body, whereas NAT2 is expressed predominantly in the intestine and liver [243]. In the intestine, both NATs are expressed in the GIT from esophagus to colon [55]. NAT2 is predominantly present in epithelial cells of the human intestine and involved in activation of compounds passing through this organ. The lung and urothelium of the urinary bladder express NAT1 and NAT2, while these are not expressed in the human kidneys [55,243]. In the human brain, the homologous enzymes NAT8L and NAT14 are involved in *N*-acetylaspartate synthesis [244]. NAT1 is expressed in human skin epidermal keratinocytes [56].

8.3.2.1.3 Glutathione S-Transferases. Glutathione *S*-transferases (GSTs) utilize glutathione (GSH) to form conjugates with a wide range of structurally different electrophilic substrates. This conjugation provides protection against cellular/organ toxicity [245]. GSTs are induced by diverse chemical compounds, such as isothiocyanates (such as benzylisothiocyanate, allylisothiocyanate, and sulforaphane), phenobarbital, 1,4-bis[2-(3,5-dichloropyridyloxy)]benzene, pregnenolone-16α-carbonitrile, 3-methylcholanthrene, 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin, BNF, butylated hydroxyanisole, ethoxyquin, oltipraz, fumaric acid, coumarin, dexamethasone, thiazolidinediones 1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole, 12-*O*-tetradecanoylphorbol-13-acetate, glyphosate, citrus triterpenoids (nomilin, isoobacunoic acid, and deacetyl nomilin), rambo (0.6% permethrin), cinnamon, cardamom, protocatechuic acid, myristicin, and so on [246–255]. The gene expression of GSTs is mediated by multiple receptors, viz, constitutive androstane receptor (CAR), PXR, AhR, nuclear factor E2 related factor (Nrf2), peroxisome proliferator-activated receptor-α/γ (PPAR α/γ), and CAATT/enhancer-binding protein (C/EBP) β [249,256,257]. Caffeic acid phenethyl ester selectively inhibits GSTs in the presence of tyrosine [258].

The mammalian GSTs have been very well characterized and classified as GST-α (GSTA), GST-μ (GSTM), GST-π (GSTP), and GST-θ (GSTT) subtypes based on structural conformation of protein, immunological identity and their susceptibility to inducers and inhibitors [245,259]. The GST isozymes reported in humans are GSTA1-4, GSTM1-5, GSTP1, GSTT1, and GSTT2 [260]. GSTA1, GSTA2, GSTM1 GSTM2, and GSTP1 are inhibited by polyphenolic compounds, such as ellagic acid and curcumin. GSTM1 and GSTM2 are also inhibited by genistein, kaempferol and quercetin [261].

GSTAs, GSTMs, and GSTPs are mainly expressed in the human GIT [262,263]. Overall, the activity of GSTs and expression of GSTA in the GIT increases in the following order: duodenum > stomach > sigmoid colon > transverse colon [58]. GSTA4, GSTM3, and GSTT1 are organ specific and located in the small intestine [148]. Duodenum shows higher GST activity than the colon [264]. GSTPs are highly expressed in the stomach, and their expression decreases from the proximal to distal direction [58]. The contents of GSTA and GSTP in the stomach are 4.5 ± 0.5 and $16.5 \pm 0.7\,\mu g/mg$ and in duodenum are 20.0 ± 0.7 and $11.2 \pm 0.5\,\mu g/mg$, respectively [58]. The main role of

GSTs in GIT is to detoxify electrophilic compounds ingested with foods (e.g., quinones and 4-hydroxyalk-2-enals), dietary supplements, and orally administered medicaments [265]. There is a report where 2(3)-*tert*-butyl-4-hydroxyanisole (BHA) induced GST by 2- and 15-folds in the mice stomach and small intestine, respectively [266]. PAHs and phenobarbital also induce GST in the intestine [267].

Multiple GSTs are expressed in the human lungs [268]. The GSTM isoforms, GSTM1 and GSTM3, are collectively expressed at 89.3 ± 27.8 ng/mg and GSTP1 at 762 ± 27.9 ng/mg. The combined expression of GSTA1 and GSTA2 in the lung is 80.8 ± 17.6 ng/mg [269]. Similar to GIT, GST expression in the lungs is induced by BHA, providing protection against lung cancer induced by PAHs [266]. GSTA, GSTM, and GSTP are expressed in the human kidneys and GSTA isoforms are highly expressed (50–70%) in the PCT, loop of Henle, and CD. GSTM and GSTP isoforms are expressed in DCT, Bowman's capsule, and CD [31,67,270]. GST isozymes in kidney are inhibited competitively by bromosulphophthalein and noncompetitively by bilirubin and haematin [60]. GSTM3, GSTM5, and GSTP are expressed in the human brain. GSTP is mainly localized in choroid plexus, pia-arachnoid, tanycytes, astrocytes, and ependyma of the brain, while GSTM3 is localized in astrocytes [61,271,272].

The reported activity of GSTs in epidermis, dermis, and whole skin is 27.5 ± 2.8, 44.2 ± 3.0, and 48.3 ± 3.05 nmol conjugate/min/mg protein, respectively [64]. GSTA, GSTM, and GSTP are expressed in the human skin cytosol, where GSTM is involved in detoxification of environmental toxicants that lead to skin allergies [64,65,273]. GSTP mRNA is expressed in cultured keratinocytes and fibroblasts of the human skin [274].

8.3.2.1.4 Sulfotransferases. Sulfotransferases (SULTs) are responsible for *O*- and *N*-sulfation of xenobiotics. Sulfation of molecules usually increases water solubility, often accompanied by a decrease in biological activity. SULTs are present either as membrane-bound or cytosolic enzymes. Membrane-bound SULTs are responsible for the sulfonation of peptides, proteins, lipids, and glycosaminoglycans, while cytosolic SULTs metabolize endogenous steroids, bile acids, neurotransmitters, and xenobiotics [275]. Three families of SULTs, that is, SULT1 (SULT1A1, SULT1A3, SULT1B1, SULT1C1, SULT1C2, SULT1C3, and SULT1E1), SULT2 (SULT2A1 and SULT2B), and SULT4 (SULT4A1) have been identified in humans, and SULT3 has primarily been reported in zebra fish [276–279].

SULT1 and its subtypes are responsible for the sulfonation of planar phenolic molecules such as estradiol, thyroid hormones, and xenobiotics [280]. SULT1A1, SULT1A3, SULT1C1, and SULT1E1 are involved in the sulfation of small neutral phenols, monoamine neurotransmitters, *N*-hydroxy-2-acetylaminofluorene, and 17β-estradiol [280–283], respectively. SULT1C2 catalyzes sulfonation of thyroid hormone [284]. SULT2s are responsible for the sulfonation of hydroxyl groups of steroids, such as androsterone, allopregnanolone, and dehydroepiandrosterone [280]. For example, SULT2A1 metabolizes 3α- and 3β-hydroxysteroids as well as aliphatic hydroxyls of xenobiotics, whereas SULT2B1 is involved in selective sulfonation of 3β-hydroxysteroids [281].

After the liver, human intestine has been reported to have highest SULTs activity, followed by the lungs and the kidneys [220,285]. The SULT subtypes reported in the human intestine are SULT1A1, SULT1A3, SULT1B1, SULT1E1, and SULT2A1, with the order of expression being: SULT1B1 (2400 ± 1300 ng/mg) > SULT1A3

(2000 ± 1100 ng/mg) > SULT1A1 (1300 ± 650 ng/mg) > SULT1E1 (490 ± 470 ng/mg) > SULT2A1 (390 ± 130 ng/mg) [286]. SULT1C2 is identified at mRNA level in the adult stomach [278]. The total expression of SULTs in the human intestine cytosol has been reported to be 7800 ± 4600 ng/mg, higher than their expression in the liver (5960 ± 1400 ng/mg) [286]. SULT1A1, SULT1A3, and SULT1B1 are expressed throughout the GIT; SULT1C1 is found in the stomach, while SULT1E1 and SULT2A1 are detected in the jejunum, ileum, and colon [68]. SULTs exhibit intersubject variability and do not exhibit any consistent trend across the intestine. In some subjects, SULT expression is higher in the central part, while in others it is higher at either end of the intestine [287,288]. SULTs are induced by methotrexate in Caco-2 cells and by tamoxifen in the rat intestine [289,290]. Isoetharine, isoprenaline, ethinyloestradiol, and paracetamol undergo sulfate conjugation in GIT [236].

SULT1A1, SULT1A3, SULT1B1, SULT1E1, and SULT2A1 have been detected in the human lungs. While total content of SULTs in the lung is reported to be 290 ± 130 ng/mg, the individual contents of SULT1A1, SULT1A3, SULT1B1, SULT1E1, and SULT2A1 subtypes are 60 ± 50, 60 ± 80, 40 ± 20, 110 ± 110, and 30 ± 20 ng/mg, respectively [286]. SULT1C3 is present in the fetal lungs [278]. In the human kidneys, high concentration of SULTs is reported in the cytoplasm of PCT and specific subtypes are expressed in CD and medulla [31]. Total SULT content in kidney is 430 ± 270 ng/mg. The expression of SULT1A1, SULT1A3, SULT1B1, and SULT2A1 is 170 ± 90, 120 ± 70, 130 ± 110, and 5 ± 10 ng/mg, respectively, whereas expression of SULT1E1 in kidney is below the limit of quantitation [286]. SULT1C2 and SULT1C3 are expressed in the fetal kidney and SULT1C2 in the adults' kidneys [278].

Human brain expresses SULT1A1, SULT1A3, SULT1C2, SULT1E1, SULT2A1, SULT2B1, and SULT4A1 [69–72]. SULT1A1 is located in cytosol of the cerebellum, occipital, and frontal lobes, whereas SULT1A3 is present in cytosol of superior temporal gyrus, hippocampus, and temporal lobe. SULT1A1 is involved in the metabolism of small phenols and SULT1A3 metabolizes catecholamine neurotransmitters [70]. The location of SULT1E1 and SULT2B1 in the human brain is not specified [71,291]. SULT4A1 is located in the cortex, substantia nigra, cerebellum, pituitary, and brainstem; hence, it regulates functions and neurochemistry of different regions of the brain [72].

SULTs are present in the human scalp skin and skin fibroblasts [292,293]. The subtypes include SULT1A1, SULT1A3, SULT1E1, and SULT2B1 [73,74]. SULT2B1b is localized in the granular layer of skin epidermis and involved in synthesis of cholesterol sulfate, which is a critical regulator of keratinocyte differentiation and desquamation, and is a well-known mediator of barrier homeostasis [294,295]. Parabens inhibit SULTs, leading to prolonged estrogenic effects in skin, thus providing antiaging benefit [296].

8.3.2.1.5 Other Transferases. Carboxyltransferase (CT), thiopurine *S*-methyltransferase (TPMT), catechol-*O*-methyltransferase (COMT), and γ-glutamyltransferase (γ-GT) have been detected in extrahepatic sites. CT is expressed in PCT of the kidney and is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) [31]. TPMT, a cytosolic enzyme, is expressed in RBCs, kidneys, lungs, and brain, apart from the liver and is responsible for the S-methylation of thiopurines such as 6-mercaptopurine, azathioprine, and 6-thioguanine [297,298]. Naproxen, mefenamic acid, and tolfemic acid are noncompetitive inhibitors of this DME [216].

COMT is a phase II enzyme that is highly expressed in liver, kidneys, intestine, and brain (postsynaptic neuron) in both cytoplasmic-soluble and membrane-bound forms [216] and is mainly expressed in the right inferior frontal gyrus and intraparietal sulcus of the brain [75,299]. Compounds with a catechol moiety, for example, catecholestrogens and catechol-containing flavonoids, are substrates of COMT. It introduces the methyl group in catecholamine, which is donated by *S*-adenosyl-L-methionine (SAM) [299]. COMT is involved in inactivation of catecholamine neurotransmitters, viz, dopamine, epinephrine, and norepinephrine, which can ultimately lead to behavioral problems, psychiatric disorders, chronic pain, and cancer [216,300,301]. The enzyme also plays a key role in metabolism of 3,4-dihydroxyphenyl-L-alanine (L-DOPA) [302]. Other specific reactions catalyzed by COMT include conversion of dihydroxyphenylethylene glycol (DOPEG) to methoxyhydroxyphenylglycol (MOPEG), and 3,4-dihydroxymandelic acid (DOMA) to vanillylmandelic acid (VMA) [303]. Entacapone increases bioavailability of L-DOPA by inhibiting COMT both peripherally and centrally and also by blocking conversion of dopamine into 3-methoxytyramine [216,304].

γ-GT is present in lungs, kidneys, brain, spleen, heart, and seminal vesicles [77,305–309]. This enzyme is primarily expressed in the PCT of kidney, which plays an important role in the transport of amino acids through a sequence of reactions forming a "gamma-glutamyl cycle" [310]. This enzyme also releases glutamate from drug–GSH adducts, leaving behind conjugates, which cause nephrotoxicity. It is irreversibly inhibited by acivicin [305].

8.3.2.2 Epoxide Hydrolases. Epoxide hydrolases (EHs) are phase I enzymes that metabolize exogenous and endogenous epoxides to vicinal diols, which are subsequently eliminated in a conjugated form [311,312]. EH enzymes have broad substrate specificity, including epoxide derivative of PAHs, anticonvulsant drugs, and steroids. On the basis of their molecular weights, subcellular localization, and substrate specificity, these are classified into five subgroups, viz, hepoxilin EH, leukotriene A4 hydrolase, cholesterol EH, microsomal EH, and soluble epoxide hydrolase (sEH) [312]. These have been subject of intensive investigations because their inhibition protects heart, brain, and kidneys against injury [80,313–316]. EHs are expressed in bronchial epithelial cells of lung and provide protection against development of lung cancer by hydrolyzing carcinogenic products of PAHs [317]. Lung EHs metabolize epoxyetraenoic acid (EET), which is responsible for blood pressure regulation [318]. Low levels of this enzyme have been reported in cytosolic fractions of the kidney [78]. EHs are differentially expressed in cerebral blood vessels and brain parenchyma, demonstrating their involvement in metabolism of vasodilator EETs into inactive diol metabolite in the brain [79,319]. EHs are found in epidermis, dermis, epithelial cells, and fibroblasts in the human skin [81–84]. These are reported to metabolize benzo(α)pyrene-4,5-oxide and *trans*-stilbene oxide in rat skin microsomes [320].

8.3.2.3 Flavin-Containing Monooxygenases. CYPs and flavin-containing monooxygenases (FMOs) have partially overlapping substrate specificities, although they may or may not generate the same metabolites. For example, FMOs exhibit highest catalytic activity toward pesticides, such as carbophenothion, methiocarb, and aldicarb and result in the generation of a sulfone metabolite [321]. In comparison, these pesticides are metabolized by CYPs into sulfoxide and sulfone [322]. Apart from qualitative and quantitative differences in the generation of metabolites, FMOs

and CYPs also exhibit differential stereoselectivity [323,324]. These enzymes are mainly involved in the metabolism of nucleophillic xenobiotics that contain nitrogen, sulfur, and phosphorous heteroatoms, for example, trimethylamine, sulindac, and methionine [88,325–328]. FMOs are of five subtypes, viz FMO1, FMO2, FMO3, FMO4, and FMO5 [329]. Their expression varies across extrahepatic tissues.

The relative expression of FMO subtypes in the human intestine is in the following order: FMO5 > FMO2 > FMO1 > FMO4 > FMO3 [86]. FMO1 is expressed in the human small intestine to a level of 2.9 ± 1.9 pmol/mg microsomal protein [329]. In the human lungs, FMOs are located in nonciliated bronchiolar epithelial (Clara) cells [330]. Among these, FMO2 is specifically expressed in lung, and primary amines and alkyl sulfides are important substrates for it [331,332]. The relative expression of FMO3, FMO4, and FMO5 in the human lungs as compared to the liver is ~4.5%, ~7% and ~4%, respectively. The overall order of expression of FMO subtypes in lung is FMO2 > FMO5 > FMO3 > FMO4 > FMO1 [86].

The primary site of the expression of FMO1 and FMO4 is the human kidneys [87]. Reported expression levels of FMO1, FMO3, and FMO5 in the human kidneys are 5.8 ± 2.3, 0.5 ± 0.4, and 2.4 ± 1.4 pmol/mg, respectively [96]. The expression of FMO1 varies from 5.0 ± 1.7 to 7.7 ± 2.4 pmol/mg of protein. It is involved in the metabolism of nitrogen- and sulfur-containing nucleophiles [96]. In human kidneys, FMO3 has very low expression (~3.7% of liver), while FMO4 is expressed moderately [93]. Renal FMOs are involved in the biotransformation of 5-HT3 antagonists, viz, tropisetron and meperidine, into *N*-oxide metabolite [86,333]. In brain, FMOs are localized predominantly in neuronal cell bodies in magnocellular reticular nuclei, colliculi, and substantia nigra with relatively constant expression [88]. These enzymes are responsible for the metabolism of CNS drugs, for example, imipramine, fluoxetine, and chlorpromazine [334]. Relative expression of FMO subtypes in the human brain is in the order of FMO2 > FMO5 > FMO4 > FMO3 > FMO1 [86]. In the rat brain, FMOs metabolize *N*,*N*-dimethylaniline, methimazole, thiabenzamide, and antidepressant drugs such as imipramine and fluoxetine [88,335]. FMO1 and its polymorphs have potential influence on nicotine metabolism and hence, modulate its concentration in the brain [87,336].

In the skin, FMOs are localized in the epidermis, sebaceous glands, and hair follicles, with their basic role being detoxification of xenobiotics to which the skin is exposed [94]. FMO1 is expressed in epidermis and dermis and FMO3 in dermis, while FMO4 and FMO5 are expressed almost equally in total skin, dermis, and epidermis [89,94,95]. Another study has also reported the presence of FMO1, FMO3, FMO4, and FMO5 in the human skin, and these subtypes were found to play an important role in the metabolism of phorate [337].

8.3.2.4 Monoamine Oxidases. Monoamine oxidases (MAOs) are involved in the oxidative deamination of a range of monoamines, including 5-hydroxytryptamine (serotonin), histamine, and catecholamines (viz, dopamine, noradrenaline, and adrenaline), to yield respective aldehydes by liberating ammonia and hydrogen peroxide [338]. These enzymes are located predominantly in the outer membrane of mitochondria, with low concentrations associated with microsomal fractions [99]. MAOs are abundantly expressed in organs with direct exposure to the environment, for example, lungs, GIT, and liver [338]. In humans, MAO-A and MAO-B are expressed, with the order of expression of MAO-A being small intestine ≥ placenta ≥ lungs ≥ muscle > kidneys

$>$ brain $\geq$ spinal cord $\geq$ meninges $\geq$ liver $>$ spleen $>$ adrenal glands, and MAO-B: small intestine $>$ kidneys $\geq$ liver $>$ adrenal glands $>$ heart $>$ spinal cord $>$ lungs. The combined MAO activity in different parts of the brain is in the order: frontal cortex $>$ locus coeruleus $>$ temporal cortex $\geq$ posterior pensylvian cortex-supramarginal gyri $>$ anterior pensylvian cortex-opercular gyri $\gg$ hippocampus and thalamus [97]. MAO-A is present in catecholaminergic neurons (cells of the substantia nigra, the locus coeruleus, and the periventricular regions of the hypothalamus); while predominant expression of MAO-B is in serotonergic neurons (dorsal raphe nucleus), astrocytes, lateral and posterior hypothalamic regions, and platelets [99,100]. These MAOs are nonselectively inhibited by stilbene-like derivatives [339]. In different organs, MAO-A is selectively inhibited by clorgyline, toloxatone, and cimoxatone, while MAO-B is inhibited by selegiline (L-deprenyl) [340–342]. The MAO enzymes are expressed in nerves around hair follicles, cutaneous nerve fibers beneath the epidermis, and human skin fibroblasts [101–104].

8.3.2.5 Additional Non-CYP Enzymes. β-Glucuronidase (β-Gluc), alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), aldose reductase (AR), myeloperoxidase (MPO), and GSH reductase are additional non-CYP enzymes present in extrahepatic sites. β-Gluc is located in the brush border epithelium and microflora of human GIT, lung alveolar macrophages, spleen, and placenta [105,106,343,344]. It is responsible for the cleavage of glucuronide complexes and for the liberation of the active moiety for reabsorption, in cases, leading to enhanced drug action [49]. In gut, β-Gluc is responsible for the hydrolysis of exogenous and endogenous β-glucuronides produced in the liver by UGT (e.g., morphine glucuronide conjugates), aiding in enterohepatic reabsorption [105].

ADHs are cytosolic dimeric metalloenzymes involved in the metabolism of ethanol to aldehydes in the presence of nicotinamide adenine dinucleotide [118]. ADHs are located in the gingiva, tongue, esophagus, stomach, and colon in GIT. These do not show any specific pattern of expression from distal to proximal end of the human GIT but are highly expressed in esophagus and stomach [118]. They have also been reported to be expressed in the human lungs [107]. In the human kidneys, ADHs are mainly located in epithelial tubuli, glomeruli, and collecting tubules. Low content of ADHs is also reported in adrenal glands, neurons of the cerebral cortex, hypothalamus, infundibular stalk of the pituitary, and purkinje cells of the brain cerebellum [108,111]. In the human skin, ADH is localized in the epidermis, sebaceous glands, and hair follicles and is involved in detoxication and toxication of compounds that can cause allergic contact dermatitis, such as *trans*-cinnamaldehyde and *trans*-cinnamic alcohol [110,345].

Human ADHs have been divided into following five classes based on structural and catalytic features: Class I (α-ADH, β-ADH, and γ-ADHs); Class II (π-ADH), Class III (χ-ADH), Class IV (μ-ADH or σ-ADH), and Class V (resembles Class I, named as αα-isozyme) [112,118,346]. Class I ADH mRNA is widely distributed in most tissues, including brain and placenta, although it is abundantly expressed in hepatic region and plays major role in the first-step metabolism of ethanol. The expression of Class II and Class V mRNA is mainly limited to hepatic tissues, with low mRNA concentrations of Class II detected in stomach, pancreas, and small intestine. Class V enzymes demonstrate similar distribution in fetal kidneys and small intestine. The distribution pattern of Class III mRNA is consistent with those of housekeeping enzymes, while expression of Class IV mRNA is restricted to the stomach [112].

ALDHs are responsible for the oxidation of aldehydes generated during retinoic acid biosynthesis and alcohol metabolism and also for the metabolism of amino acids, biogenic amines, steroids, lipids, carbohydrates, and drugs into their respective carboxylic acids [347]. Ten types of ALDHs (ALDH1-10) are known [115,118]. ALDH1, ALDH2, and ALDH6 are expressed in the gut; ALDH3 and ALDH7 in the lung; and ALDH4, ALDH6, ALDH7, and ALDH9 in the kidney [115]. In the GIT, ALDHs are located in gingiva, tongue, esophagus, and stomach. Like ADHs, these enzymes are also highly expressed in esophagus and stomach [118]. Expression of ALDHs in the lung is increased by carcinogenic aldehydes found in cigarette smoke [348]. In the kidney, ALDH enzymes are located in cortex tubules and provide protection against toxicity of aldehydic metabolites, for example, chloroacetaldehyde, a metabolic product of ifosfamide [349]. In the human brain, expression of ALDHs is in the order of spinal cord > corpus callosum > subthalamic nucleus > medulla > thalamus > amygdale > cerebral cortex > substantia nigra > hippocampus > caudate nucleus > temporal lobe > cerebellum > putamen > frontal lobe > occipital pole [350]. These are reported to be involved in metabolism of γ-aminobutyraldehyde [350]. ALDH enzymes are located in the epidermis, sebaceous glands, and hair follicles of the human skin and play an important role in the metabolism of exogenous aldehydes. ALDH1, ALDH2, and ALDH3 are detected in different regions of the human skin. ALDH1 and ALDH3 are predominantly localized in the epidermis and dermal appendages [117], while ALDH2 is localized in the epidermis and hair follicles of the human skin [120].

AR is a NADPH-dependent oxidoreductase enzyme that is involved in the reduction of a variety of aldehydes and carbonyls, including monosaccharides. Substrates for AR include isocortisol, isocorticosterone, aromatic aldehydes, arylalkylaldehydes, and so on [351]. It is primarily known to catalyze reduction of glucose to sorbitol, the first step in the polyol pathway of glucose metabolism. The second and last step in the pathway is catalyzed by sorbitol dehydrogenase, which helps in the oxidation of sorbitol to fructose [352]. The aldose reductase reaction, responsible for sorbitol production, is important for the function of various organs in the body. For example, fructose produced from sorbitol is used by the sperm cells and is also used as an energy source for glycolysis and glyconeogenesis [353]. Incidentally, AR is also linked with toxicities, e.g. there is persistent increase in glucose levels, like in diabetes. Being hyperosmotic, the presence of sorbitol increases pressure inside various organs and hence leads to retinopathy, nephropathy, neuropathy, and other diabetic complications [354–356]. Retinopathy is linked to the presence of AR in the mural cell of retina and lens in the eyes [357,358]. AR in the human small intestine is coded HSI-AR and is reported to catalyze the reduction of carotene [121]. In the human kidneys, AR mRNA is expressed in the papilla of epithelial, endothelial, interstitial, and thin limb cells, connecting tubules, cortical CDs, and medullary CD. Weak expression is reported in the outer medulla, cortex, Bowman's capsule, and the glomerular tuft [122]. This enzyme is also reported in the human brain and involved in catalysis of NADPH-dependent reduction of physiological and xenobiotic aldehydes [123].

MPO is a phase I peroxidase enzyme present in the lysosome of neutrophils and exists in high concentration in the lung [124]. MPO is involved in the activation of benzo(α)pyrene and aromatic amines in tobacco smoke to generate carcinogenic free radicals [124,359]. 4-Aminobenzoic acid hydrazide is a specific irreversible inhibitor of MPO [360].

8.4 FACTORS INFLUENCING EXPRESSION OF EXTRAHEPATIC DMEs

Genetic polymorphism, age, gender, pathophysiological conditions, inborn errors in metabolism, environmental pollutants, and food contribute to the expression and activity of DMEs.

8.4.1 Genetic Polymorphism

Genetic polymorphism is defined as differential expression of genes, that is, having multiple alleles in different populations. Polymorphism in genes may be inherited and/or occur because of environmental factors. The study of alleles provides information on differences in levels of enzymes, which also helps to predict interpopulation variation in susceptibility to diseases. Genetic polymorphism of CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 alter their activities, resulting in diminished efficacy or increased toxicity of certain drugs [361,362]. For example, poor metabolizing phenotype of CYP2D6 results in dose-dependent toxicity of debrisoquine, perhexilene, and phenacetin, while the extensive metabolizing phenotype leads to therapeutic failure of codeine and selected antidepressant drugs in different populations [363]. Alterations in genes including CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, GSTM1, GSTT1, GSTP1, NAT, and SULT have the potential to contribute to toxicities, including metabolic activation of procarcinogens, leading to development of carcinogenicity in extrahepatic organs [364–366]. Table 8.2 summarizes studies on genetic polymorphism of DMEs in extrahepatic tissues, mainly with relevance to the development of cancer.

8.4.2 Age and Gender

The expression of DMEs, especially CYPs, is greatly influenced by both age and gender. Usually, extrahepatic expression of CYPs is lower in neonatal and pediatric tissues, relative to the adults, for example, CYP1A1 is not found in kidneys of neonates [403]. In the fetal duodenum, CYP3A4 activity is absent, and a statistically significant increase in expression was observed from two weeks to 17 years of age [404]. The expression of duodenal CYP3A4 is maximum in young females and decreases by around 20% in postmenopausal women [405]. In the kidney, CYP3A4 and CYP3A5 are present at gestational age of eight weeks [406]. MAO-B activity is low at birth, remains constant in childhood, and then increases with age [407]. The level of EHs in fetal lungs is comparatively lower than the adult lungs [408]. Table 8.3 lists additional instances where DMEs are higher in fetus and neonates than adults.

Among the examples of the influence of gender, CYP2E1 is less active in women than men, with no gender differences in activities of CYP1A2, CYP2C19, CYP2D6, and CYP3A4 [412]. However, Paine *et al*. [405] reported higher CYP3A4 expression in the small intestine of men than women. In different studies on smokers, women had higher expression of CYP1A1, CYP1A2, and CYP3A4 in the lung as compared to men [413–415]. Higher CYP3A4 expression was associated with the metabolism of major lung procarcinogens/carcinogens to generate reactive oxygen species (ROS) or reactive metabolites, thus exacerbating the susceptibility to carcinogenicity [415].

Both age- and gender-dependent differences have also been reported in the expression and activity of GSTs, with women having higher expression in the distal colon, as

TABLE 8.2 Relationship of Genetic Polymorphism of DMEs with the Development of Cancer in Extrahepatic Organs

Enzyme	Organ with Expression of Polymorphic Gene	Genotype/Allele	Outcome	Population (State/Country)	References
CYP1A1	Esophagus	*CYP1A1 exon 7* polymorphism*(Val/Val)*	Slightly increased risk of cancer	Not specified (Taiwan)	367
		CYP1A1 MspI polymorphism	No association with the development of cancer	Not specified (Taiwan)	367
		CYP1A1 (Ile/Ile)	No association with the development of cancer	Japanese	368
		CYP1A1 MspI, exon7	No association with the development of cancer	Caucasian	365
	Stomach	*CYP1A1 MspI*	No significant influence on the development of cancer	Chinese (Dalian)	369
		CYP1A1 Val	Increased probability of cancer on smoking	Chinese (Yangzhong)	370
	Colorectal	*CYP1A1 Ile/Val*	Significantly associated with the development of cancer	Hungarian (Hungary)	371
		CYP1A1 MspI, Ile462Val	Not associated with the development of cancer	Not specified (State of Utah)	372
		*CYP1A1*2B*	Increased frequency of cancer development	Caucasian	373
	Lung	*CYP1A1 w1/m1, CYP1A1 w2/m2*	Increased risk of squamous cell carcinoma	Caucasian	374
		MspI	Increased susceptibility to cancer development on the exposure to environmental pollutants	Chilean	375
		*CYP1A1*2C, CYP1A1 MspI*	Increased cancer susceptibility	North Indian	376

(*continued overleaf*)

TABLE 8.2 ***(continued)***

Enzyme	Organ with Expression of Polymorphic Gene	Genotype/Allele	Outcome	Population (State/Country)	References
		CYP1A1 Msp I	Increased risk of cancer development	South Indian	377
		*CYP1A1*2B (MspI* and*Ile462Val)*	Increased risk of cancer development	Caucasian	378
CYP2E1	Esophagus	*c1/c2, c2/c2*	No association with the development of cancer	Japanese	368
	Colorectal	*RsaI*	Decreased risk of cancer development	Not specified (Hawaii)	379
		96-bp insertion	Increased risk of cancer development	Not specified (Hawaii)	379
		*c*2	Increased risk of cancer development	Hungarian	380
		RsaI	No association with the development of cancer	Australian	381
		*c*2/*c*2	Increased susceptibility of the development of rectal cancer on interaction with environment, and on smoking and drinking of alcohol	Chinese	382
		*c*1/*c*2	Significantly associated with the development of cancer	Hungarian	371
	Lung	*RsaI*	No association with the development of cancer	Caucasian	383

		RsaI	No association with the development of cancer	African-American	383
		RsaI	Decreased risk of cancer development	Not specified (Hawaii)	384
		RsaI	Decreased risk of cancer development	Chinese	385
		c and *c*2	No correlation with the development of cancer	Chilean	375
		RsaI and *DraI*	Can be protective to cancer development	Caucasian	386
GSTM1	Esophagus	Null	No association with development of cancer	Japanese	368
	Stomach	Null	Increased risk of cancer development	Chinese (Yangzhong)	370
		Null	Increased risk of cancer development	Chinese	387
	Colorectal	Null	Increased risk of cancer development	Spanish	388
		Null	Increased risk of cancer development	Caucasian	373
	Lung	Null	Increased susceptibility to cancer development on exposure to environmental pollutants	Chilean	375
		Null	Increased susceptibility of cancer development	French Caucasian	386
		Null	No association with cancer risk	Caucasian	389

(*continued overleaf*)

TABLE 8.2 ***(continued)***

Enzyme	Organ with Expression of Polymorphic Gene	Genotype/Allele	Outcome	Population (State/Country)	References
		Null	Increased susceptibility of cancer development	African-American	389
		Null	Increased susceptibility of cancer development	North Indian	390
		Null	Increased susceptibility of cancer development	South Indian	391
	Urinary bladder	Null	Increased susceptibility of cancer development	Caucasian (Germany)	392
	Ovarian	Null	No evidence of correlation	Australian	393
GSTT1	Stomach	Null	Increased in risk of cancer development	Spanish	388
	Lung	Null	No association with the development of cancer	Caucasian	389
SULT	Lung	*SULT1A1*2*	Increased risk of lung cancer development	Caucasian	394
	Urinary bladder	*SULT1A1*	Reduced risk of urinary bladder cancer development	Not specified	395
NAT1	Stomach	*NAT1*10*	Increased risk of gastric cancer development	Japanese	396
	Colorectal	*NAT1*10*	Polymorphism not significant risk factor for colorectal adenocarcinoma	Japanese	396
		*NAT1*10*	Increased risk of cancer development	Caucasian (Staffordshire area of England).	397

	Lung	*NAT1*10, NAT1*11*	Increased risk of cancer development	French Caucasian	398
		*NAT1*3, NAT1*4*	Increased risk of cancer development	French Caucasian	398
		*NAT1*14, NAT1*15*	Increased risk of cancer development	French Caucasian	398
	Urinary bladder	*NAT1*10*	Increased risk of cancer development	Australian	399
		*NAT1*10*	Decreased risk of cancer development	Caucasian	400
NAT2	Colorectal	*NAT1*10*	No significant association found between polymorphism and gastric/colorectal cancer development	Japanese	396
	Lung	Not specified	No significant association found between polymorphism and lung cancer development	Not specified (France)	398
	Urinary bladder	*NAT2*4*	Decreased risk of cancer development	German	400
EH	Lung	Combined *Exon 3* and *4* variant allele	Decreased risk of cancer development due to reduced EH activity	African-American	401
		Combined *Exon 3* and *4* variant allele	Not much promising results for reduced risk of cancer development	American Caucasian	401
		Exon 3 variant allele	Provides protective effect against cancer development	Non-hispanic whites	402
		Exon 4 variant allele	Increased risk of cancer development	Non-hispanic whites	402

TABLE 8.3 Examples of Higher Expression of DMEs in Early Years of Human Life as Compared to Adulthood

Enzyme	Age Group	Organ(s)	Anticipated Outcome	References
CYP1A1	Fetus	Brain	—	409
	8 and 21 weeks gestational age	Lung	—	403
CYP1B1	Fetus	Kidney, thymus, and lung	—	403,409,410
CYP2B6	Neonates	Kidney	Renders neonates more vulnerable to ifosfamide induced nephrotoxicity	404
CYP2R1	Fetus	Brain	—	409
CYP2W1	Fetus	Lung and kidney	—	409
CYP3A4	Neonates	Kidney	Renders neonates more vulnerable to ifosfamide-induced nephrotoxicity	404
GSTP1	Fetus and neonates	Lung	—	411
GSTA1/A2	20 Weeks gestational age	Kidney (nephron)	—	411
SULT1A3	Fetus (18–25 weeks)	Kidney	—	411
FMO1	Fetus	Brain	—	86

compared to men [264]. In this study, the GST activity increased with age in women, while it remained constant in men. Reversibly, expression of GSTM1 did not change in women with age but decreased in men on aging. Also, expression of GSTP1 in distal and proximal colon of women (50–70 years) was higher than men and women below 50 years.

The expression of ADHs in gastric mucosa of women has been reported to be less than that of men. ADH activity decreased in men with increasing age, while values in women between 41 and 60 years of age were higher than those between 20–40 and 61–80 years. In men of 40–50 years, gastric ADH level decreased significantly and became almost similar to that of women of the same age. There was reduced ADH activity in men between 20 and 40 years, who consumed large quantities of alcohol [416,417].

8.4.3 Pathophysiological Conditions and Inborn Errors of Metabolism

The expression of DMEs in extrahepatic organs can be altered by disease states, and certain diseases such as cancer are provoked because of alterations in the enzyme levels. Inborn errors of metabolism result in expression of inactive enzymes [418]. CYPs may be downregulated because of (i) inflammation in response to tissue damage, (ii) infection, (iii) burns, (iv) trauma, (v) tumors, and (vi) autoimmune diseases. Infectious agents, such as hepatitis A, influenza A/B, herpes simplex, HIV, helicobacter pylori, plasmodium falciparum, and so on, also modulate CYP-dependent biotransformation of drugs in humans [418]. Table 8.4 lists disease conditions and inborn errors

TABLE 8.4 Changes in the Expression of Enzymes in Extrahepatic Organs as a Result of Pathophysiological Conditions and Inborn Errors of Metabolism

Organ(s)	Disease/Infecting Agent/Inborn Error of Metabolism	Enzyme	Expression of mRNA/Proteins	References
Esophagus	Squamous cell carcinoma	CYP1A1, CYP1A2, CYP2E1, CYP1B1, CYP2C8, and CYP2C9	Expressed only in tumor cells	419–421
		CYP2B6 and CYP3A5	Increase	419–421
		CYP3A4	Decrease	419
	Adenocarcinoma	CYP2J2	Expressed only in tumor cells	419
Stomach	Foveolar epithelium with intestinal metaplasia of stomach	CYP3A4	Increase	422
	Gastric carcinoma	CYP1B1 and CYP2J2	Expressed only in tumor cells	419,420
		CYP2W1	Increase	419,420
	Chronic gastritis (caused by *Helicobacter pylori*)	ADH	Decrease	423,424
Small and large intestine	Celiac disease	CYP3A	Decrease	425–427
		CYP1A	Decrease	427
	Crohn's disease	CYP3A4 and CYP3A5	Increase	425
	Inflammatory bowel disease	CYP3A4 and CYP3A5	Increase	419
	Colon adenocarcinoma	She	Decrease	428
		CYP1B1	Expressed only in tumor cells	419,420
		CYP2J2 and CYP3A5	Increase	419,420
	Colorectal carcinoma	CYP2A6, CYP2B, CYP2F1, and CYP2W1	Decrease	419
		CYP2S1 and CYP2U1	Increase	419
	Colorectal adenomatous carcinoma	CYP2C8	Increase	419
	Ulcerative colitis	CYP3A4, CYP2C9, and CYP3A7	Dysregulation	425
	Taenia taeniformis infection	CYP1A1 and CYP2B1	Increase	418

(*continued overleaf*)

TABLE 8.4 **(*continued*)**

Organ(s)	Disease/Infecting Agent/Inborn Error of Metabolism	Enzyme	Expression of mRNA/Proteins	References
Nasopharynx	Nasopharyngeal carcinoma	CYP1B1	Increase	419
Lung	Non-small-cell lung cancer	CYP1A1 and CYP2B7	Decrease	419
	A549 adenocarcinoma cell lines	CYP1A1	Decrease	419
	Bronchioloalveolar carcinoma	CYP1A1	Decrease	419
	Pulmonary squamous cell carcinoma	CYP1B1 and CYP2J2	Expressed only in tumor cells	419,420
	Lung carcinoma	CTP2W1	Expressed only in tumor cells	419
		CYP3A7 and CYP4B1	Decrease	419
	Respiratory viral infection	CYP1A	Decrease	429
	Squamous cell lung cancer	ALDH1A1 and ALDH3A1	Increase	348
Kidney	Renal cell carcinoma	CYP1A1, CYP3A1, CYP3A2, and CYP3A5	Increase	31
		CYP1B1	Increase	420
		γ-GT	Increase	31
		Quinone oxidoreductase	Decrease	31
		sEH, CYP2C9, CYP2C8, and CYP2J2	Decrease	428
	Clear cell carcinoma, transitional cell carcinoma	CYP1B1	Expressed only in tumor cells	419
	Uremia	CYP2D6	Decrease	31
	Adenocarcinoma	CYP4A2	Decrease	31
	Acute renal failure	γ-GT	Increase	31
	Diabetes mellitus	UGT2B7	Decrease	430
Bladder	Bladder carcinoma	CYP2D6 and CYP4B1	Increase	419
		CYP2W1	Decrease	419
	Transitional cell carcinoma	CYP1B1	Expressed only in tumor cells	419,420
Brain	Glial cell tumor	CYP1B1	Expressed only in tumor cells	419
	Alzheimer's disease	CYP27 and CYP46	Redistribution	15
	Parkinson's disease	CYP2D6	Decrease	15

	Inflammation followed by ischemic brain injury (astrocytes of hippocampus)	CYP2E1	Increase	429,431
		CYP1A1	Decrease	429,431
	Inflammation due to trauma-evoked head injury	CYP4F4 and CYP4F5	First decrease and then increase after two weeks	418
Heart	Dilated cardiomyopathy	CYP1A1	Detected in right ventricle, ascending aorta, pulmonary aorta, and right atrium. In normal patients, it is detected only in left ventricle	11,12
		CYP2B6 and CYP2B7	Detected in right ventricle and aorta	11
		CYP4B1	Detected in right ventricle	11
		CYP2D6	Detected only in right ventricle	11
		CYP2C8 and CYP2C9	Induced following ischemic injury	432
Different organs	Systemic lupus erythematosus that results in skin rashes and inflammation of multiple organs	CYP2D6	Decrease	418
Inborn errors of metabolism with effect on different organs	Congenital adrenal hyperplasia (adrenals glands)	CYP11A1, CYP11B1, CYP11B2, CYP17, and CYP21	Autosomal recessive disorder	3
	Vitamin-D-dependent rickets (bones)	CYP27B1 and 25-hydroxy D_3 1α-hydroxylase	Autosomal recessive disorder	3
	Primary congenital glaucoma (eyes)	CYP1B1	Autosomal recessive eye disorder (deletions, insertions)	3
	Sjögren–Larsson syndrome (skin and nervous system)	ALDH10	Autosomal recessive disorder	3

of metabolism, which can alter expression of DMEs and defects in enzyme genes, respectively.

8.4.4 Food

Another category that influences expression of CYPs in various extrahepatic organs is food. For example, chronic intake of char-grilled meat induces CYP1A1 in the intestine, and this is linked with potentiating the risk of intestinal cancer [433]. The nature of food also affects GST expression, for example, GSTA and GSTP were induced in duodenum on intake of vegetables and GSTT1 in gastric mucosa was induced on the consumption of certain fruits. Citrus fruits induced GST activity in the rectal mucosa, and a brassica vegetable also leads to induction of GSTM1 [434]. However, no reports exist on food-dependent changes in colonic GST activity. A majority of commonly used food products, such as potato, onion, garlic, spices, rice, and bread, do not change DME activities significantly [58].

8.5 ROLE OF EXTRAHEPATIC DMEs IN BIOACTIVATION AND DEACTIVATION OF XENOBIOTICS

DMEs in extrahepatic organs play an important role in bioactivation of drugs/prodrugs/precarcinogens and/or deactivation of drugs/metabolites/carcinogens. For example, terfenadine (a nonsedating antihistaminic prodrug) is metabolized by CYP3A4 in the intestine, to the active moiety, fexofenadine (Fig. 8.4). The active metabolite acts on H1 receptors at different sites in the body, resulting in pharmacological activity [198]. Similarly, metabolism of cyclophosphamide is directly responsible for its therapeutic activity and also for toxicity. The initial activation step involves oxidation of the heterocyclic ring to produce 4-hydroxycyclophosphamide, which is in spontaneous equilibrium with its cyclic tautomer aldophosphamide. Acrolein is spontaneously eliminated from aldophosphamide to yield phosphoramide mustard, an active alkylating agent. 4-Hydroxycyclophosphamide, acrolein, and phosphoramide mustard in the presence of CYPs and other oxidative enzymes are responsible for the pharmacological activity as well as toxicity of the drug (Fig. 8.5) [435]. Another example is of sulindac, a sulfoxide prodrug, which is metabolized in kidney into inactive sulfone and bioactive sulfide (Fig. 8.6). The formation of

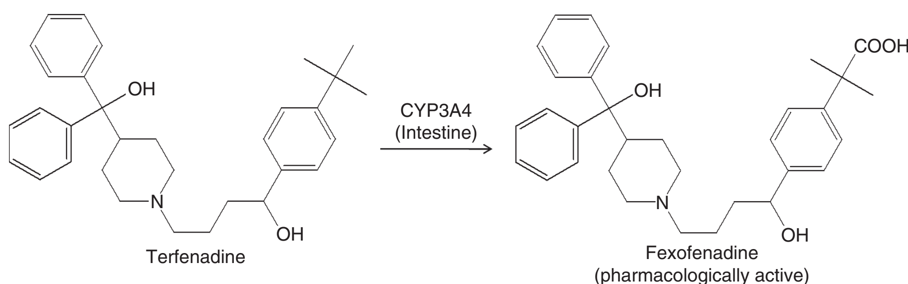

Figure 8.4 Bioactivation of terfenadine in the GIT.

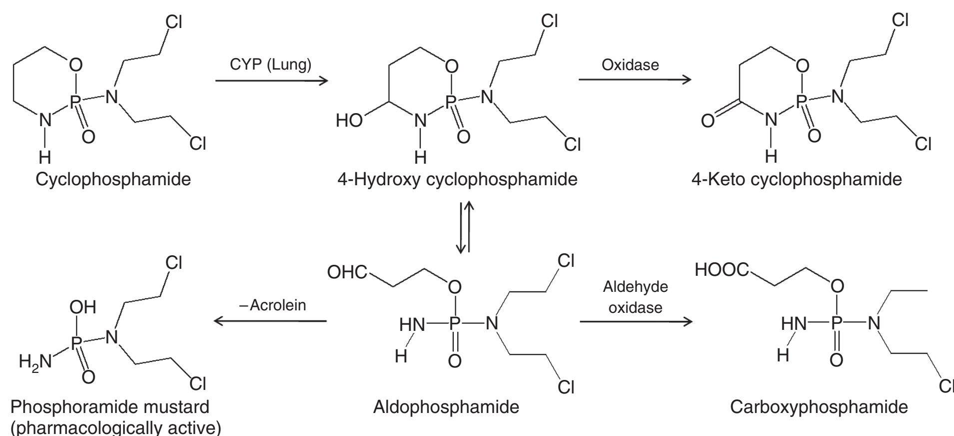

Figure 8.5 Metabolism of cyclophosphamide in the lung.

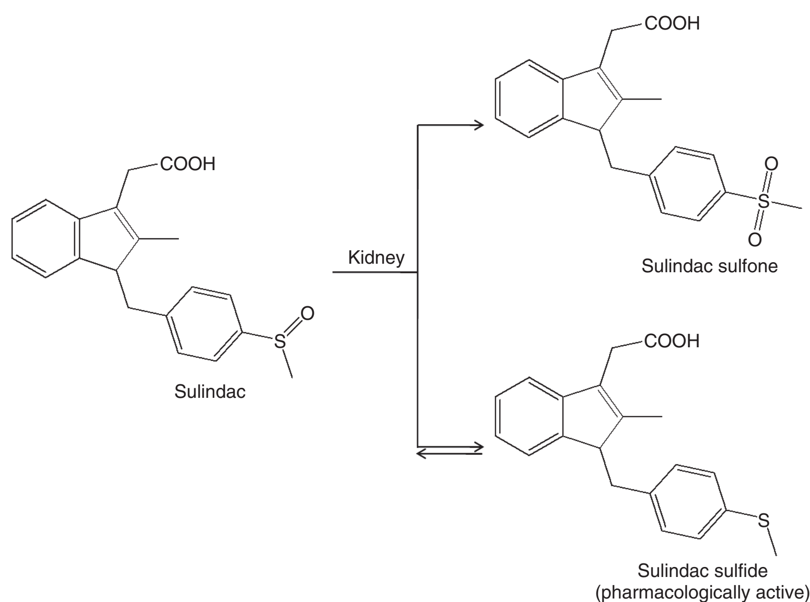

Figure 8.6 Metabolism of sulindac in the kidneys [436].

the latter is reversible, therefore, the kidney rapidly interconverts active sulfide back to inactive sulfoxide [436]. The reaction is reported to be mediated in humans by kidney microsomal FMOs [437]. Similarly, codeine is metabolized into morphine by CYP2D6 in the brain (Fig. 8.7), which is responsible for the analgesic effect of the former [438]. Additional examples of bioactivation and deactivation of drugs in GIT, lungs, kidneys, and brain, along with their metabolites, are listed in Table 8.5.

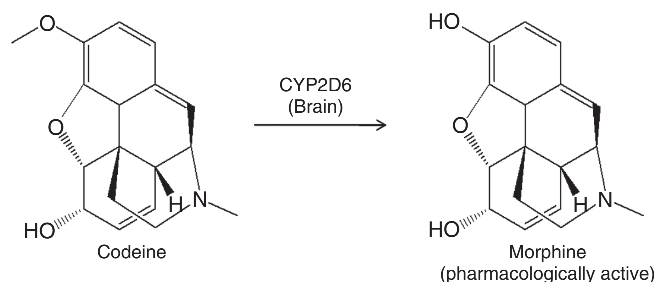

Figure 8.7 Metabolic bioactivation of codeine in the brain.

8.6 SIGNIFICANCE OF EXTRAHEPATIC METABOLISM

The metabolism of drugs in extrahepatic organs results in alteration of systemic bioavailability and toxicity. Inhibition/induction of DMEs in extrahepatic tissues and organs by the drugs can alter pharmacokinetic/pharmacodynamics of other concomitantly administered drugs. These effects have significant impact on the overall clinical outcome of the therapy.

8.6.1 Bioavailability

The therapeutic action of a drug is determined by the dose achieved at the target site in the body. The latter in turn is determined by the amount of the substance absorbed, which further depends on its bioavailability. The bioavailability of drugs can be limited by their absorption from the GIT epithelium and/or through first-pass metabolism. Although the major site for the first-pass metabolism is liver, GIT is a significant contributor, as it presents a very large area for the metabolism, with numerous DMEs being expressed along its length. For example, Marier *et al*. [543] explored the contribution of rabbit liver and intestine on the elimination rate of different enantiomers of propranolol. At a concentration of 5.8 μM, *R*(+) propranolol was metabolized faster in the intestine in comparison to the liver. Likewise, the bioavailability of inhaled drugs is significantly affected by their metabolism in the lung. In addition, factors such as age, sex, food, disease state, and interindividual variation were found to influence the bioavailability of drugs and xenobiotics, owing to increase or decrease in the expression of DMEs [544,545].

8.6.2 Toxicity

Drug-induced organ toxicity is not only dose-dependent but also a result of the generation of reactive metabolites, which include electrophiles and/or free radicals. The latter have the potential to interact with nucleophiles, such as DNA and proteins. The mechanism of reactive metabolite-induced toxicity is shown in Fig. 8.8 [546]. Toxicity can be significantly alleviated as a result of the binding of reactive metabolites to GSH, but once most of the GSH gets consumed, reactive metabolites exceed a limit, leading to significant toxic effects.

The wide distribution of DMEs in different organs provides the possibility for generation of reactive metabolites across the body and hence, the widespread toxicity.

TABLE 8.5 **Examples of Drugs that Undergo Bioactivation and Deactivation in Extrahepatic Tissues**

Organ	Substrate	DME	Metabolic Product(s)	Outcome/Significance	References
Gastrointestinal tract	Chlorpromazine	CYP	*S*-oxide, *N*-oxide, 7-hydroxyl, desmethyl, and didesmethyl chlorpromazine	Deactivation and first-pass metabolism	439,440
	Carbamazepine	CYP	10,11-Epoxide and 10,11-*trans* dihydrodiol carbamazepine	Deactivation and first-pass metabolism	441,442
	Astemizole	CYP	*O*-Desmethyl astemizole	Deactivation and first-pass metabolism	145
	Benzo(α)pyrene	CYP1A1	Benzo(α)pyrene-7,8-dihydrodiol	DNA adduct formation	443
	Astemizole	CYP2J2	Astemizole *O*-demethylation	First-pass metabolism	145
	Alprazolam	CYP3A4	Alprazolam-4-hydroxylation	Deactivation and first-pass metabolism	444,445
	Terfinadine	CYP3A4	Fexofenadine	Bioactivation	198
	Indinavir	CYP3A4	Oxidative metabolite	Deactivation	446
	Simvastatin	CYP3A4	—	Deactivation and first-pass metabolism	442
	Buspirone	CYP3A4	—	Deactivation and first-pass metabolism	442
	Carvedilol	CYP3A4	Oxidative metabolite	Biotransformation	447
	Diazepam	CYP3A4	—	Deactivation and first-pass metabolism	442
	Sirolimus	CYP3A4	Secorapamycin	Biotransformation	448
	Felodipine	CYP3A4	—	Deactivation and first-pass metabolism	442
	Clindamycin	CYP3A4	Clindamycin sulfoxide	Biotransformation	449
	Saquinavir	CYP3A4	—	Deactivation and first-pass metabolism	442
	Nicardipine	CYP3A4	—	Deactivation and first-pass metabolism	442
	Flurazepam	CYP3A4	Mono- and didesetyl flurazepam	Deactivation and first-pass metabolism	450
	Midazolam	CYP3A4 and CYP3A5	1′-Hydroxymidazolam	Deactivation and first-pass metabolism	444,451,452
	Verapamil	CYP3A4	—	Deactivation and first-pass metabolism	442
	Nifedipine	CYP3A4	Oxidized nifedipine	Deactivation and first-pass metabolism	444,453,454
	Nisoldipine	CYP3A4	BAY o 3199 and BAY r 9425	Biotransformation	455

(*continued overleaf*)

TABLE 8.5 (*continued*)

Organ	Substrate	DME	Metabolic Product(s)	Outcome/Significance	References
	Lovastatin	CYP3A4	6′β-Hydroxy and 6′-exomethylene lovastatin	Deactivation and first-pass metabolism	456,457
	Fentanyl	CYP3A4	*N*-Dealkylated fentanyl	Deactivation and first-pass metabolism	458
	Cyclosporine	CYP3A4	Hydroxylated and *N*-methylated cyclosporine	Deactivation and first-pass metabolism	459
	Tacrolimus	CYP3A4	13-*O*-Demethyl and 13,15-*O*-demethyl tacrolimus	Deactivation and first-pass metabolism	460
	Methadone	CYP3A4	2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, 2-ethyl-5-methyl-3,3-diphenylpyraline	Deactivation	461
	L-α-Acetylmethadol	CYP3A4	L-α-Acetyl-*N*-normethadol, L-α-acetyl-*N*,*N*-dinormethadol	Bioactivation	461
	Ebastine	CYP3A4	Desalkylebastine	Deactivation	462
	Ritonavir	CYP3A4	N-Demethylation, oxidation of methylthiazolyl, hydroxylation of isopropyl side chain, and 2-(1-methylethyl)thiazolylmethyl group	Biotransformation	463
	Pravastatin	CYP3A4 and CYP3A5	3′α, 5′β, 6′β-Trihydroxypravastatin, sulphated pravastatin, 3′α-iso-pravastatin.	Deactivation and first-pass metabolism	456
	Oxycodone	CYP3A4 and CYP3A5	*N*-Demethyled oxycodone	Deactivation and first-pass metabolism	464
	Prasugrel	CYP3A and carboxylesterase 2	Thiol-containing active metabolites	Bioactivation	465

Quinidine	CYP3A62	3-Hydroxy quinidine	Deactivation and first-pass metabolism	466
Amiodarone	CYP3A1, CYP3A2, and CYP1A1	Desethylamiodarone	Deactivation and first-pass metabolism	467
Benzamidoxime	Reductase	Benzamidine	—	468
Guanoxaben	Reductase	Guanabenz	—	468
Ethanol	ADH	Acetaldehyde	First-pass metabolism	469
Polychlorinated biphenylol	UGTs	Glucuronide conjugate	Deactivation	470
Bisphenol A	UGTs	Glucuronide conjugate	Biotransformation	471
Galangin	UGTs	Galangin glucuronide	Deactivation	472
Kaempferol	UGTs	Kaempferol glucuronide	Deactivation	472
Indomethacin	UGTs	Indomethacin glucuronide	Deactivation	473
Paracetamol	UGTs	Glucuronide conjugate	Deactivation	474
Salbutamol	UGTs	Glucuronide conjugate	Deactivation	462
Salmeterol	UGTs	Glucuronide conjugate	Deactivation	462
Bambuterol	UGTs	Glucuronide conjugate	Deactivation	462
Formoterol	UGTs	Glucuronide conjugate	Deactivation	462
Fenoterol	UGTs	Glucuronide conjugate	Deactivation	475
Losartan	UGTs	Glucuronide conjugate	Deactivation	476
1-Naphthol	UGTs	Glucuronide conjugate	Deactivation	477
Biochanin A	UGT	Glucuronide conjugate	Deactivation	478
Raloxifene	UGT	Glucuronide conjugate	Deactivation	478
Scutellarin	UGTs and β-glucuronidase	Scutellarein	Bioactivation	479
Baicalein	UGT and SULT	Glucuronidation and sulfation of baicalein	Biotransformation	480
Clioquinol	SULT1A3	Sulphated clioquinol	Biotransformation	481

(*continued overleaf*)

TABLE 8.5 (*continued*)

Organ	Substrate	DME	Metabolic Product(s)	Outcome/Significance	References
	Fenthion	FMO1	Fenthion sulfoxide	Biotransformation	325
	Methiocarb	FMO1	Methiocarb sulfoxide	Biotransformation	325
	Cefpodoxime proxetil	Choline esterases	Cefpodoxime	Bioactivation	482,483
	O-Isovaleryl-propranolol	Esterase	Propranolol	Bioactivation	484
	L-751,164 (prodrug of potent fibrinogen receptor antagonist)	Esterase	L-742,998 (active drug)	Bioactivation	485
	Glycovir	Esterase	SC-48334 (active metabolite)	Bioactivation	486
	Timolol maleate	Esterase	Timolol	Bioactivation	487
	Levobunolol	Ketone reductase	Dihydrolevobunolol	—	487
	5-Aminosalicylic acid	NAT	*N*-Acetyled-5-aminosalicylic acid	Deactivation	488
	Ambamide	Amine oxidase	*p*-Carboxybenzene sulphonamide	Deactivation	489
	Isoprenaline	COMT	*O*-Methyl isoprenaline	Deactivation and first-pass metabolism	490,491
	Terbutaline	Not defined	Sulphate conjugate	Deactivation and first-pass metabolism	492
	3-Chloro-1,2-propanediol fatty acid esters	Not defined	Hydrolytic metabolites	Detoxification	493
	Halofantrine	Not defined	Desbutylhalofantrine	Bioactivation	494
	Daidzein	Not defined	Equol	Bioactivation	495
	Cycloastragenol	Not defined	Glucuronide conjugates and oxidative metabolites	Deactivation and first-pass metabolism	496
	Hesperetin	Not defined	Hesperidin	Deactivation and first-pass metabolism	497

	Enalapril	Not defined	Enalaprilat	Bioactivation	498
	Cyadox	Not defined	Cyadox-1-monoxide	Biotransformation	499
Pulmonary system	Phorate	CYP	(+) Phorate sulfoxide	Detoxification	324,500
	Nilutamide	CYP	Amine and hydroxylamine metabolite	Reactive metabolite generation	501
	Benzo(α)pyrene	CYP1A1	Benzo(α)pyrene-7,8-dihydroepoxide	Metabolic activation by epoxide hydroxylase and CYP1B1 followed by the formation of DNA adducts, leading to lung cancer	502,503
	NKK	CYP1A1	Keto aldehyde (major), keto alcohol (minor)	Carcinogenic product	20
	3-Methylindole	CYP1A1, CYP2F1, CYP2A13, and CYP4B1	3-Methyleneindolenine	Alkylates DNA and induces cell death through apoptosis	504
	Benzo(α)pyrene	CYP1B1	Benzo(α)pyrene-7,8-dihydroepoxide	Carcinogenic product leading to mutation in *p*53 gene in lung	503
	Benzo(α)pyrene-7,8-dihydroepoxide	EH	(±)-Benzo(α) pyrene-*trans*-7,8-dihydrodiol	—	503
	(±)-Benzo(α) pyrene-*trans*-7,8-dihydrodiol	CYP1B1	Benzo(α)pyrene-7,8-dihydrodiol-9,10-epoxide	Carcinogenic product leading to mutation in *p*53 gene in lung	503

(*continued overleaf*)

TABLE 8.5 (*continued*)

Organ	Substrate	DME	Metabolic Product(s)	Outcome/Significance	References
	AFB1	CYP2A13	AFB1-8,9-epoxide	Mutation of *p*53 and then inactivation leading to cancer, DNA and protein adducts	10,505,506
	NKK	CYP2A6	Keto alcohol, keto aldehyde	Carcinogenic product	20
		CYP2A13	Keto alcohol (major), keto aldehyde (minor)	Carcinogenic product	20
		CYP2B6	NKK-*N*-oxide	Detoxification process of NKK in human lung	507
	1,1-Dichloro-ethylene	CYP2E1	2,2-Dichloro-acetaldehyde, 1,1-dichloroethylene-epoxide	Covalent binding with proteins/DNA, causes Clara cell toxicity	508,509
	Butadiene	CYP2E1	Butadiene oxide	Not defined	159
	Chlorzoxazone	CYP2E1	6-Hydroxylated chlorzoxazone	Not defined	159
	N-Nitrosodime-thylamine	CYP2E1	Demethylated *N*-nitrosodimethylamine	Not defined	159
	p-Nitrophenol	CYP2E1	Hydroxylated *p*-nitrophenol	Not defined	159
	Trichloroethylene	CYP2E1 and CYP2F	Chloral hydrate	Clara cell toxicity	508
	Styrene	CYP2F	Epoxide styrene	Carcinogenic product	172
	Naphthalene	CYP2F	Naphthalene 5,6-epoxide, naphthalene 7,8-epoxide	Carcinogenic product	510
	Benzene	CYP2E1, CYP2B1, and CYP2F	Benzene oxide	May be responsible for the generation of tumors	511
	Nifedipine	CYP3A	Oxidative metabolite	Not defined	159
	4-Ipomenol	CYP4B1	Epoxide	DNA/protein covalent binding	512,513
	Benzamidoxime	Reductase	Benzamidine	—	468
	Guanoxaben	Reductase	Guanabenz	—	468

	Phorate	FMO2	(−) Phorate sulfoxide	Detoxification	500
Urinary system	Paracetamol	CYP2E1	NAPQI	Necrosis	514
	Cyclosporine A	CYP3A5	Hydroxylated cyclosporine (AM9)	Deactivation	178,515
	Benzamidoxime	Reductase	Benzamidine	—	468
	Guanoxaben	Reductase	Guanabenz	—	468
	Niflumic acid	UGT2B7	Glucuronide conjugate	Deactivation	516
	Paracetamol	UGT	Glucuronide conjugate	Deactivation	517
	Zidovudine	UGT	Glucuronide conjugate	Deactivation	518
	Almokalant	UGT	Glucuronide conjugate	Deactivation	519
	Diflunisal	UGT	Glucuronide conjugate	Deactivation	520
	Trichloroethylene	GST	*S*-(1,2-Dichlorovinyl)glutathione	Detoxification	521
	(*R*)- or (*S*)-2-bromoisovalerylurea	GST	Glutathione conjugation	Detoxification	522
	S-(6-Purinyl) glutathione	GGT	*S*-(6-Purinyl)-L-cysteine	Bioactivation	523
	S-(6-Purinyl)-L-cysteine	β-Lyase	6-Mercaptopurine	Bioactivation	523
	6-Mercaptopurine	Xanthine oxidase	6-Thioxanthine	Deactivation	523
	MeDDC[a]	FMO1	MeDDC sulfine, MeDTC, MeDTC sulfoxide	Bioactivation	524
	Sulindac sulfide	FMO1	Sulindac sulfoxide	Deactivation	329,436
	Paracetamol	FMO1	Sulfate conjugate	Deactivation	517,525
	Fenthion	FMO1	Fenthion sulfoxide	Biotransformation	325
	Methiocarb	FMO1	Methiocarb sulfoxide	Biotransformation	325
	Methionine	FMO3	Methionine sulfoxide	—	328
	Tropisetron	FMO	*N*-Oxide metabolite	Biotransformation	86,333
	Meperidine	FMO	*N*-Oxide metabolite	Biotransformation	86,333

(*continued overleaf*)

TABLE 8.5 ***(continued)***

Organ	Substrate	DME	Metabolic Product(s)	Outcome/Significance	References
Central nervous system	Nicotine	CYP2B1, CYP2A6, and CYP2B6	Cotinine	Deactivation	21,526,527
	Selegiline	CYP2B6 and CYP2C19	L-Methamphetamine, L-amphetamine, desmethylselegiline	Deactivation	185
	Imipramine	CYP2C18	*N*-Demethylated imipramine, imipramine-*N*-oxide	Deactivation	528
	Alprazolam	CYP3A43	α-Hydroxylated alprazolam	Biotransformation	194,529
	Imipramine	CYP4F6	10-Hydroxylated imipramine	Deactivation	528
	Codeine	CYP2D6	Morphine	Deactivation	438
	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine	CYP2D6	—	Detoxification	180
	Benzamidoxime	Reductase	Benzamidine	—	468
	Guanoxaben	Reductase	Guanabenz	—	468
	Propofol	UGT1A6	Propofolglucuronide	Deactivation	231
Skin	Capsaicin	CYP	Vanillylamine, vanillic acid	Biotransformation	530
	Hesperetin	UGT	Hesperetin glucuronide	Biotransformation	531
	Fluroxypyr methyl ester	Esterase	Fluroxypyr	Acid metabolite	204
	Fluroxypyr methylheptyl ester	Esterase	Fluroxypyr	Acid metabolite	204
	Amethocaine	Esterase	*p*-(Butyl)aminobenzoic acid	Biotransformation	532
	O-Acyl haloperidol ester	Esterase	Haloperidol	Bioactivation	533
	Acyclovir valerate	Esterase	Acyclovir	Bioactivation	534

	Sulfamethoxazole	NAT	*N*-Hydroxy and *N*-acetyl metabolites	Bioactivation	535
	Paraphenylene-diamine	NAT1	Monoacetyl paraphenylenediamine	Biotransformation	56
	Benzocaine	NAT	*N*-Acetylbenzocaine	Biotransformation	536
	Phorate	FMO	Phorate sulfoxidation	Biotransformation	337
	Triclosan	UGT	Glucuronide conjugate	Biotransformation	537
	Triclosan	SULT	Sulfate conjugate	Biotransformation	537
	Minoxidil	Phenol sulfotransferase	Minoxidil sulfate	Bioactivation	292,538
	Propranolol	Microsomes	4′-Hydroxypropranol	Biotransformation	539
	Theophylline	Microsomes	1,3,7-Trimethyluric acid and 1,3-dimethyl uric acid	Biotransformation	540
	Prednisolone farnesylate	Not specified	Prednisolone	Bioactivation	541
	TU-2100 [bis(*o*-carboxyphenyl ethyl ester) nonanedioate]	Not specified	—	Bioactivation	542
CVS	Glyceryl trinitrate	CYP3A4	NO	Biotransformation	16
	Isosorbide Dinitrate	CYP3A4	NO	Biotransformation	16
	Verapamil	CYP3A4, CYP3A5, CYP2C8, CYP2C18, CYP2D6 and CYP2E1	Carbinolamine, *N*-formyl, ahemiacetale, *N*-demethyl, *O*-demethylverapamil	Biotransformation	92

Abbreviations: AFB1, Aflatoxin B1; MeDDC, *S*-methyl *N*,*N*-diethyldithiocarbamate; MeDTC, *S*-methyl *N*,*N*-diethylthiocarbamate; NAPQI, *N*-acetyl-*p*-benzoquinoneimine; NKK, 4-methylnitrosamino)-1-(3-pyridyl)-1-butanone.
[a]Disulfiram metabolite generated in liver.

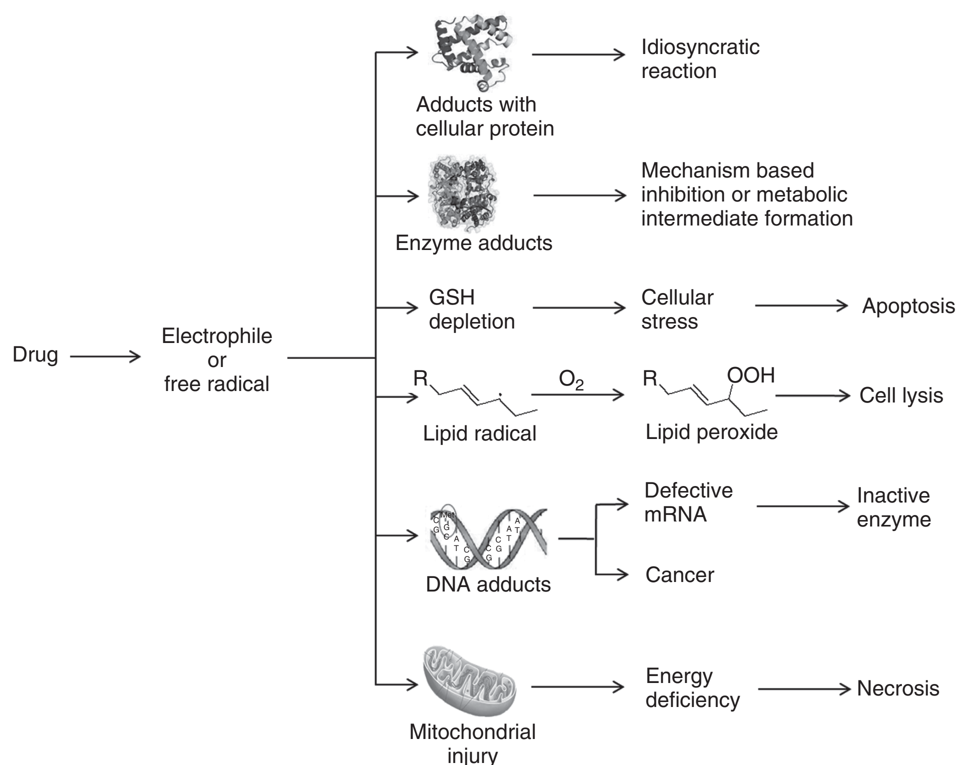

Figure 8.8 Mechanism of reactive metabolite-induced toxicity. (See color insert.)

Table 8.6 summarizes the nature of toxicity shown by different xenobiotics in extrahepatic organs, with indications on the mechanisms involved.

Since the GIT is rich in different DMEs, orally administrated drugs can be metabolized, which may lead to the generation of reactive metabolites and subsequent toxicity. For example, acrylonitrile, a dietary carcinogen, is metabolized to form reactive epoxide in intestine by CYP2E1 and to a lesser extent by CYP2B1. This metabolite is responsible for the generation of toxicity in the intestine by three pathways: (i) direct binding with nucleophillic moieties, such as DNA and proteins, and the release of cyanide (CN^-); (ii) hydrolysis followed by the release of CN^-; and (iii) interaction with sulfhydryl compounds (GSH and/or *N*-acetylcysteine) with associated release of CN^- (Fig. 8.9). This conversion of acrylonitrile to CN^- group is enhanced by phenobarbital, BNF, 4-methylpyrazole, or ethanol [547].

Like GIT, the lung is also susceptible to toxicity because of the formation of reactive metabolites. Lungs are directly exposed to air, so these come in direct contact with pollutants. Owing to abundant oxygen in lung, environmental contaminants have the potential to undergo redox reactions, resulting in the formation of oxygen superoxide radicals that can result in toxicity to the pulmonary system [580]. The lung is additionally exposed to drugs and xenobiotics through extensive cardiac output that circulates through them. Xenobiotics, such as 4-ipomeanol and 3-methylindole, are metabolized in different tissues and subsequently transported to lung through blood

TABLE 8.6 **Toxic Events Attributed to Different Xenobiotics in Extrahepatic organs, Including the Mechanisms Involved**

Organ	Xenobiotics	Enzyme	Reactive Metabolite	Mechanism	Outcome	References
Gastrointestinal tract	Acrylonitrile	CYP2E1 and CYP2B1	Epoxide intermediate	Can bind directly to nucleophillic moieties or release reactive CN^-	Carcinogenicity	547
	5-Fluorouracil	—	—	—	Apoptosis or cell cycle arrest in intestinal epithelial cells	548
Gastrointestinal tract + pulmonary system	Benzo(α)pyrene	CYP1A1, CYP1B1, CYP2C, CYP3A4, AKR1A1 AKR1C1-1 C4, and EH	Epoxide, quinone metabolites	Electrophile and free radical generation	Form covalent adducts with DNA, resulting in mutation of *p*53 gene, leading to lung carcinogenicity	7,373,502,503, 549–551
	Aromatic and heterocyclic amines	CYP1A2, CYP1A1, CYP1B1, NAT1, NAT2, SULT1A1, SULT1A2, and SULT1A3	Nitrenium ion	N-Hydroxylation, sulfonation metabolism	DNA adduct formation, resulting into carcinogenicity	55,373,552
Pulmonary system	Naphthalene	CYP2F2	$1R, 2S$- to $1S, 2R$-epoxide metabolite	Oxidative metabolism	GSH depletion, adduct formation cellular proteins, nonciliated airway epithelial cell injury	553–556

(*continued overleaf*)

TABLE 8.6 (*continued*)

Organ	Xenobiotics	Enzyme	Reactive Metabolite	Mechanism	Outcome	References
	4-Ipomeanol	CYP1A2, CYP2B7, CYP3A3, CYP3A4, and CYP2F1	Epoxide intermediate	Oxidative metabolism	Edema, congestion, and hemorrhage	513,557,558
	3-Methylfuran	CYP	—	—	Bronchiolar alkylation and necrosis of nonciliated bronchiolar cells (Clara cells)	559
	Bromobenzene	CYP	Bromobenzene-3,4-oxide	—	GSH depletion, cellular damage, and lipid peroxidation	560–562
	3-Methylindole	CYP1A1, CYP2A13, CYP2F1, and CYP4B1	Epoxides and free radical intermediates	Oxidative metabolism	Covalent binding to proteins and nucleic acids or stimulation of lipid peroxidation leads to alveolar type 1 and nonciliated bronchiolar epithelial cells injury	504,563,564
	Butylated hydroxy-toluene	CYP2B	6-*Tert*-butyl-2-[2′-(2′-hydroxy methyl)-propyl]-4-methylphenol, 4-hydroperoxy-4-methyl-2,6-di-*tert*-butyl-2,5-cyclo-hexadienone	Hydroxylation metabolism	Lung damage and elevated risk of lung tumor development	565–567
	Carbon tetrachloride	CYP	—	—	Clara and type II cell damage	561

1,1-Dichloro-ethylene	CYP2E1 and CYP2F2	2,2-Dichioroace-taldehyde, 1,1-dichloroethylene-epoxide	Oxidative metabolism	Clara cell toxicity	568
Styrene	CYP2E1 and CYP2F2	7,8-Styrene oxide	—	Tumor, Clara, and terminal bronchiole cell toxicity	569
p-Xylene	CYP and ADH	*p*-Methylbenzy-lalcohol, *p*-methylbenzal-dehyde	—	Cell destruction	570,571
α-Naphthyl-thiourea	CYP	α-Naphthylurea, atomic sulfur	—	Atomic sulfur formed in this reaction covalently binds to macromolecules, pulmonary edema	572,573
Monocrotaline (pyrollizidine alkaloids)	—	Ehrlich reactive (E+) metabolite	Activated in the liver to an Ehrlich reactive metabolite that is transported to the lung	Swelling of pulmonary capillary endothelial cells, thrombosis, and lesions of the arterial media	574,575
Bleomycin	Mixed-function oxidase	—	—	Increased lung collagen synthesis and deposition finally leads to pulmonary fibrosis	576

(*continued overleaf*)

TABLE 8.6 (*continued*)

Organ	Xenobiotics	Enzyme	Reactive Metabolite	Mechanism	Outcome	References
	Mitomycin C	NADPH:cytochrome *c* reductase and DT-diaphorase	Semiquinone radical and hydroquinone intermediate	Metabolism takes place under anaerobic conditions	Cellular toxicity	577
	Cyclophosphamide	—	4-Hydroxycyclophosphamide, acrolein and phosphoramide mustard	—	Alterations in mixed-function oxidase activity, glutathione content, and lipid peroxidation	435,578
	Paraquat	NADPH cytochrome *c* reductase	Paraquat free radicals	Elevates superoxide levels by cyclic redox mechanism	Covalent adducts with DNA and proteins or form lipid peroxide and can lead to the damage of type II pneumocytes	549,579,580
	Nitrofurantoin	Not specified	Nitro free radical	Electron reduction	Covalent adducts with proteins or spontaneously reacts with oxygen molecules to yield reduced oxygen	579,580
	NKK	CYP2A6, CYP2A13, and CYP2B6	4-Hydroxy-1-(3-pyridyl)-1-butanone, 4-oxo-1-(3-pyridyl)-1-butanone, methyldiazohydroxide	α-Hydroxylation of methyl or methylene carbon	Forms adduct with DNA can leads to carcinogenicity	20,581,582

	Aflatoxin B1	CYP2A13	Epoxide intermediate	Oxidative metabolism	Binds with DNA, RNA, proteins, and potentiates *p*53 gene mutation and inactivation, resulting in lung cancer	7,505,583
	N-Nitrosamines	CYP2E1	—	—	Cancer of lungs, nasal cavity, liver, breast and esophagus	170
	Parathion	CYP reductase and amine oxidase	Paraoxon, diethyl hydrogen phosphorothionate, diethyl hydrogen phosphate	—	Respiratory edema, respiratory failure, and cancer development	561,584,585
	Skatole	CYP2F1	—	Oxidative metabolism	Necrosis	180
Urinary system	Hexafluoropropene	GSH	*S*-(1,1,2,3,3,3-Hexafluoropropyl) glutathione	Conjugation	Undergoes further metabolism by γ-GT	586
	S-(1,1,2,3,3,3-hexafluoropropyl) glutathione	γ-GT	Cysteine *S*-conjugate	Glutamyl removal	Undergoes further metabolism by β-lyase	586
	Cysteine *S*-conjugate	β- Lyase	Thionoacyl fluoride	Lysis	Nephrotoxicity	586
	Chloroform	CYP2E1	Phosgene	Oxidative metabolism	Nephrotoxicity	587–589
	Cephaloridine	Mixed-function oxidase	Epoxide intermediate	Oxidative metabolism	Nephrotoxicity	590,591

(*continued overleaf*)

TABLE 8.6 (*continued*)

Organ	Xenobiotics	Enzyme	Reactive Metabolite	Mechanism	Outcome	References
	Aristocholic acid	CYP1A1	7-(Deoxyadenosin-*N*-6-yl) aristolactam I, 7-(deoxyguanosin-*N*-2-yl) aristolactam I, and 7-(deoxyadenosin-*N*-6-yl) aristolactam II	—	Urothelial cancer	8
	Bromobenzene	CYP	—	—	GSH depletion, cellular damage, and lipid peroxidation	562
	Parathion	CYP reductase	Paraoxon, diethyl hydrogen phosphorothionate, diethyl hydrogen phosphate	—	Nephrotoxicity	585
	Methoxyflurane	CYP2E1, CYP2A6, and CYP3A	—	Glutathione and cysteine conjugate	Nephrotoxicity	592
	Benzidine	CYP1A2	—	Oxidative metabolism	Urinary bladder cancer	180
	Cyclophos-phamide	Multiple CYP	—	Oxidative metabolism	Urinary bladder cystitis	180
Central nervous system	*N*-Methyl-4-phenyl-1, 2,3,6-tetrahy-dropyridine	MAO-B	*N*-Methyl-4-phenylpyridinium ion	—	Neuron degeneration resulting in Parkinson's disease	593

	Parathion	CYP reductase	Paraoxon, diethyl hydrogen phosphorothionate, diethyl hydrogen phosphate	—	Neurotoxicity	584,585,594
	Chlorpyrifos	—	*p*-Nitrophenol, trichloropyridinol	—	Neurotoxicity	594,595
	Amphetamine/ Metham-phetamine	—	Peroxynitrite metabolite	Free radical formation	Failure of cellular energy metabolism followed by a secondary excitotoxicity, dopaminergic neurotoxicity	596
	Paclitaxel	CYP2C8 and CYP3A5	Hydroxylated paclitaxel	—	Neurotoxicity	597
Skin	Dapsone	FMO1, FMO3, and peroxidases	Arylhydroxylamine, arylnitroso metabolites	Oxidative metabolism	Protein adduct formed	598
	Sulfametho-xazole	FMO1, FMO3, and peroxidases	Arylhydroxylamine, arylnitroso metabolites	Oxidative metabolism	Protein adduct formed	598
Central nervous system	Daunomycin	Not specified	*N*-Acetyl daunomycin	Acetylation	Cardiac arrhythmias	599

Abbreviations: AKR, aldo-keto reductase; NKK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

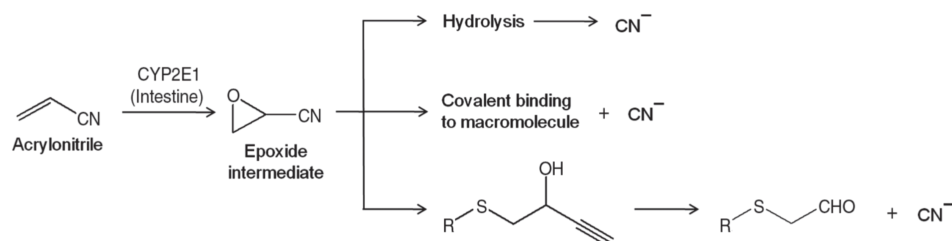

Figure 8.9 Conversion of acrylonitrile into reactive CN^- by CYP2E1 [547].

circulation, where these can result in toxicities due to covalent adduct formation [580]. Similarly, metabolic activation in lung and the formation of covalent adducts with nucleophillic species with resultant pulmonary toxicity is reported for many other xenobiotics [168]. Of special interest with respect to toxicity in both GIT and lungs are PAHs (food and air contaminants) that have the potential to result in carcinogenicity [7,373,502,503,549–551]. Inhaled air and cigarette smoke are major reasons for the exposure of lung to PAHs, while GIT is exposed to these as food contaminants. In both organs, CYP1A1, CYP1B1, EH, CYP2C, CYP3A4, aldo-keto reductase 1A1 (AKR1A1), AKR1C1, AKR1C2, AKR1C3, and AKR1C4 are responsible for the metabolic activation of PAHs, which actuate the formation of epoxide and quinone reactive metabolites, as shown in Fig. 8.10. These metabolites show genotoxicity by forming covalent adducts with DNA, resulting in mutation of *p*53 gene and hence, the development of malignancy.

Similarly, the kidneys are also susceptible to drug toxicity. For example, kidneys receive 25% of the cardiac output, although these represent only 1% of the body mass, leading to high exposure to xenobiotics. The bioactivation of xenobiotics in kidney is mediated by local DMEs, and the ability of the kidneys to concentrate xenobiotics in the tubular fluid/tubular cells can result in renal toxicities with chronic administration. Examples of xenobiotics that induce nephrotoxicity are chloroform, cephaloridine, aristocholic acid (ARA), hexafluoropropene (HFP), and methoxyflurane [8,586–591,600,601].

Aromatic and heterocyclic amines present in cigarette smoke may cause tumors in GIT, lungs, kidneys, and urinary bladder after NAT-dependent modulation. NAT1 plays role in the activation of aromatic amines through O-acetylation of *N*-hydroxyl aromatic amines (generated after metabolized by CYP1A1, CYP1A2, and CYP1B1), whereas NAT2 is associated with N-acetylation, leading to deactivation of aromatic amines. These activation and deactivation reactions are responsible for the carcinogenic effects on GIT, lungs, and urinary bladder [55,373,552,602,603], as shown in Fig. 8.11.

N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an impurity present in a fast acting opioid analgesic, meperidine, has been reported to be neurotoxic. In brain, MPTP is metabolized by MAO-B to generate 1-methyl-4-phenyl 2,3-dihydropyridinium ion ($MPDP^+$). This is finally converted into *N*-methyl-4-phenylpyridinium ion (MPP^+), as shown in Fig. 8.12. MPP^+ inhibits mitochondrial respiration in the nigrostriatal neurons and leads to an energy-deficient condition and degeneration of the latter, resulting in Parkinson's disease [593]. In this type of toxicity, MAO inhibitors and antioxidants have the potential to prevent oxidation of $MPTP^+$ to $MPDP^+$/MPP^+ in mitochondria and thus act as neuroprotective agents [604].

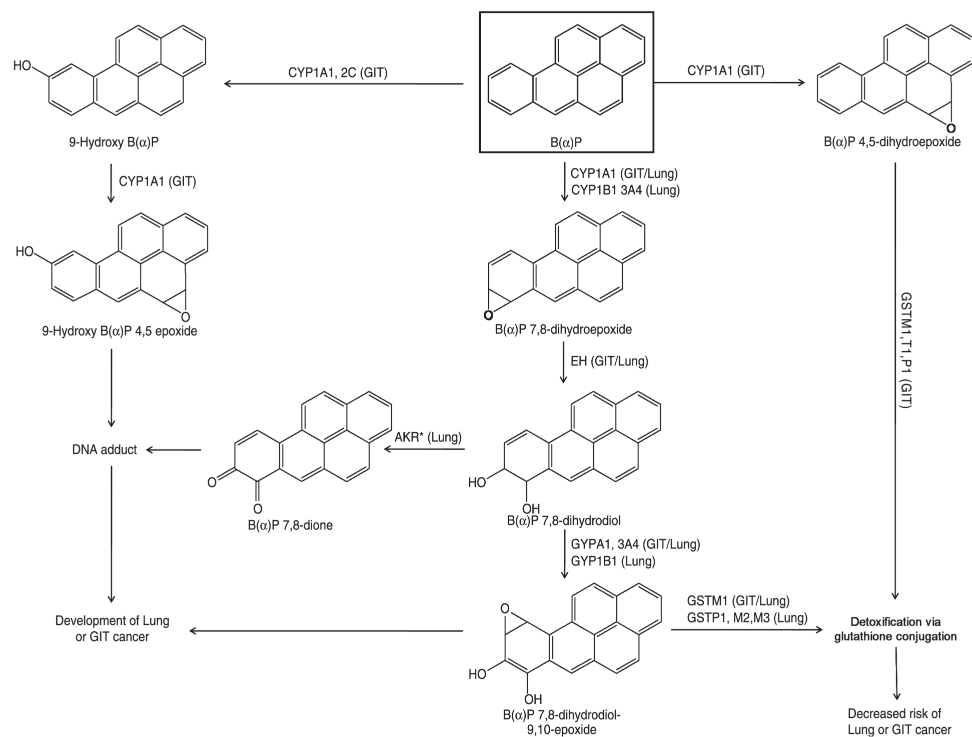

Figure 8.10 Role of DMEs present in GIT and lung in metabolic activation of a typical PAH, benzo(α)pyrene (B(α)P). * Aldo-keto reductase 1A1 (AKR1A1), AKR1C1, AKR1C2, AKR1C3 and AKR1C4.

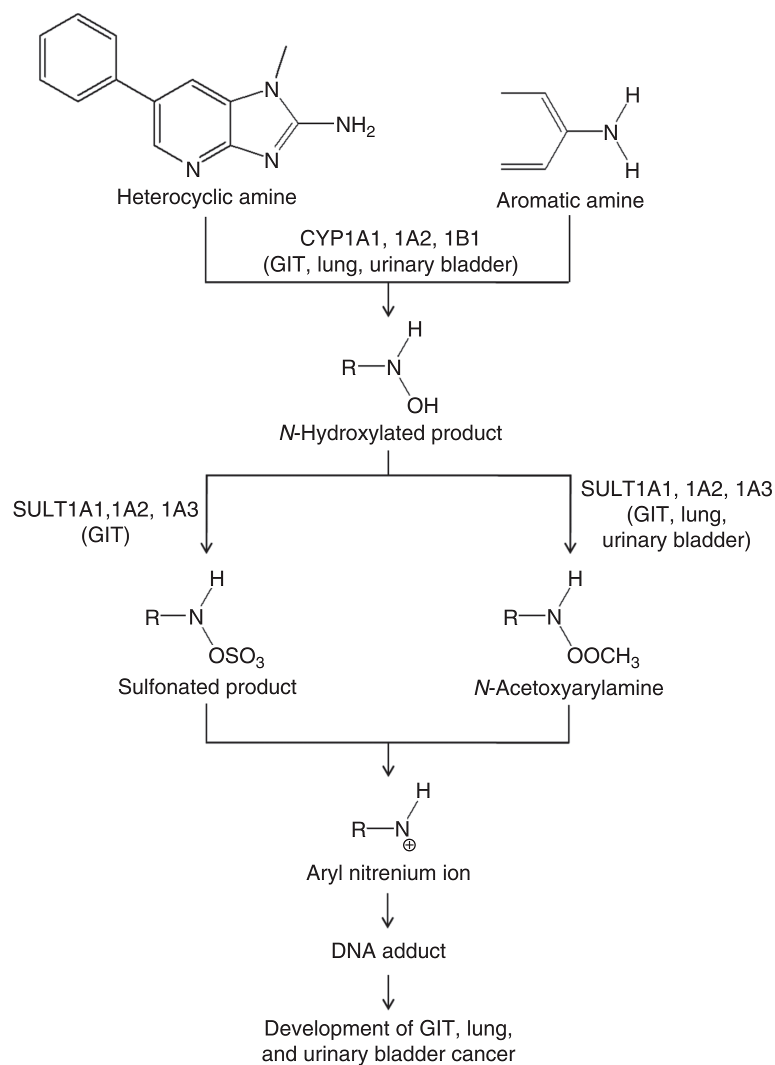

Figure 8.11 Bioactivation pathway of aromatic and heterocyclic amines depicting inception of lung/GIT/urinary bladder cancer [373].

8.6.3 Interactions in Extrahepatic Organs

Pharmacokinetic or pharmacodynamic properties of drugs may be altered in the presence of coadministrated drugs, food, and environmental toxicants. While pharmacokinetic interactions are due to changes in absorption, distribution, metabolism, or excretion of drugs, the pharmacodynamic interactions are primarily attributed to changes at the target site (synergism or antagonism). A significant proportion of drug interactions occur owing to inhibition/induction of DMEs, not only in liver but also in extrahepatic organs. For example, oral administration of rifampicin results in significant induction of CYP3A4, CYP2C8, and CYP2C9 in GIT, which leads to enhancement of the metabolism and decrease in the bioavailability of

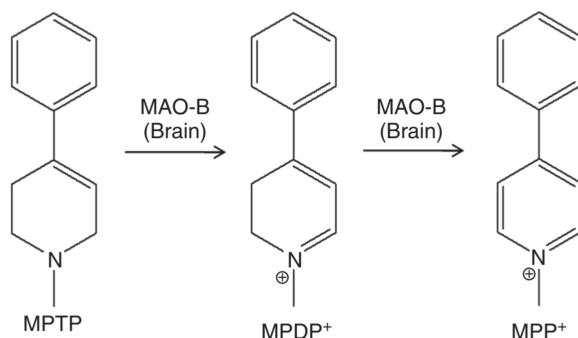

Figure 8.12 Generation of reactive *N*-methyl-4-phenylpyridinium ion (MPP^+) in the brain from *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

the coadministered CYP substrate drugs [605]. Rifampicin increases apparent oral clearance of CYP3A4 substrates, for example, *S*-verapamil, cyclosporine, and midazolam, and accordingly decreases their bioavailability [605]. Symptoms of methadone withdrawal were observed in drug addicts taking rifampicin simultaneously for the treatment of tuberculosis [606]. Similarly, St. John's wort, a herb, has been reported to interact with a number of drugs by inducing CYP3A4 in the human intestine. CYP inhibitors, such as ketoconazole, erythromycin, clarithromycin, grape fruit juice, and troleandomycin, lead to dose-dependent toxicity of CYP3A4 substrates by increasing their bioavailability [154,458,459,607]. A summary of published drug–drug interactions in extrahepatic organs are described in Table 8.7.

8.7 CONCLUSIONS

Along with the liver, DMEs are expressed in extrahepatic organs, and their levels are significantly influenced by changes in food habits, pathophysiological conditions, exposure to environmental pollutants, smoking, and so on. These enzymes are responsible for the biotransformation of xenobiotics and convert them into relatively hydrophilic metabolites that can be cleared from the body. The high allelic variation in extrahepatic DMEs contributes to the generation of diseases observed in certain populations. Biotransformation reactions involving extrahepatic DMEs are involved in the generation of reactive metabolites, such as epoxide and quinone, which lead to organ toxicity by either directly binding with nucleophilic molecules in the cells or inducing cellular stress. The involvement of extrahepatic DMEs in the metabolism of drugs influence their bioavailability when administered by oral, inhalational, and transdermal route.

Although extensive work has already been done to explore DMEs in various extrahepatic organs and characterize their role, there are still some unanswered aspects. The total contribution of extrahepatic DMEs on the bioavailability of drugs given by nonparenteral route and in drug–drug interactions and organ toxicity are not completely understood. The relative ratio of contribution of extrahepatic xenobiotic transporters and DMEs to bioavailability and clearance is also not understood. Finally, it is not

TABLE 8.7 Drug Interactions in Extrahepatic Organs and Potential Risk Factors

Organ	Substrates	DME	Interacting Agent	Cause of DDI	Potential Risk	References
Gastrointestinal tract	Cyclosporine	CYP3A4	Grape fruit juice	Enzyme inhibition	Nephrotoxicity, hypertension, cerebral toxicity	607
			Erythromycin	Enzyme inhibition	Nephrotoxicity, hypertension, cerebral toxicity	459
			Ketoconazole	Enzyme inhibition	Nephrotoxicity, hypertension, cerebral toxicity	154
			St. John's wort	Enzyme induction	Nephrotoxicity, hypertension, cerebral toxicity	608
	Saquinavir	CYP3A4	Garlic	Enzyme induction	Reduced therapeutic efficacy due to the lowering of C_{max}	609,610
	Ritonavir	CYP3A4	Garlic	Enzyme induction	Reduced therapeutic efficacy due to the lowering of C_{max}	609
	Tacrolimus	CYP3A4	Ketoconazole	Enzyme inhibition	Neurotoxic, nephrotoxicity	611,612
	Midazolam	CYP3A	Clarithromycin	Enzyme inhibition	Increased CNS depression	613
			Erythromycin	Enzyme inhibition	Increased CNS depression	614
			St. John's wort	Enzyme induction	Reduced therapeutic efficacy due to the lowering of C_{max}	615
			Grape fruit juice	Enzyme inhibition	Increased CNS depression	616
	Carvediol	CYP3A4	Grape fruit juice	Enzyme inhibition	Lethal effect in congestive heart failure patient	610
	Felodipine	CYP3A	Grape fruit juice	Enzyme inhibition	Hypotension, ankle edema	617–619
	Indinavir	CYP3A	Ketoconazole	Enzyme inhibition	Nephrotoxicity	446,620
	Fentanyl	CYP3A	Troleandomycin	Enzyme inhibition	Reduced cerebral blood flow	458,621
	Alfentanil	CYP3A	Erythromycin	Enzyme inhibition	Vasodilation and hypotension	458
			Troleandomycin	Enzyme inhibition	Vasodilation and hypotension	458

	Sildenafil	CYP3A4	Grape fruit juice	Enzyme inhibition	Hypotension, decrease in arterial pressure	607,622
	Simvastatin	CYP3A	Grape fruit juice	Enzyme inhibition	Rhabdomyolysis, acute renal failure	623
	Verapamil	CYP3A4	Rifamipicin	Enzyme induction	Reduce efficacy	605
			Grape fruit juice	Enzyme inhibition	Cardiovascular side effects	605,624
	Halofantrine	CYP3A4	Ketoconazole	Enzyme inhibition	Cardiac arrhythmia	625,626
	5-Fluorouracil	All DMEs	Nifedipine	Enzyme inhibition	Dose-dependent cardiac toxicity	627,628
	Finasteride	CYP3A4	Ketoconazole	Enzyme inhibition	—	629
	Tamoxifen	CYP2D, 3A1/2	Ondansetron	Enzyme inhibition	Pharmacokinetic interaction	630
	Hormone replacement therapy	CYP3A4	Licorice	Enzyme induction	Reduction in efficacy	610
Pulmonary system	Amiodarone	CYP1A1	PAHs	Enzyme induction	Pulmonary fibrosis	631
	Hormonal contraceptives	CYP1A1/2	PAHs	Enzyme induction	Increases chances of conceiving	632
	Inhaled corticosteroids	CYP1A1/2	PAHs	Enzyme induction	Aggravate of asthma	632
Urinary system	Diltiazem	CYP3A5	Tacrolimus	Enzyme inhibition	Nephrotoxicity	631

(*continued overleaf*)

TABLE 8.7 (*continued*)

Organ	Substrates	DME	Interacting Agent	Cause of DDI	Potential Risk	References
	Aldosterone	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	—	633
	Valproic acid	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	Bone marrow suppression	633,634
	5,6-dimethylxan-then-one-4-acetic acid, epirubicin	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	—	633
	Diclofenac	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	Risk of vascular events	633
	Naproxen	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	—	633
	Morphine, codeine	UGT2B7	Spironolactone, canrenone	Enzyme inhibition	—	633
	β-blocker diuretics	Prostaglandin synthase	Sulindac	Enzyme inhibition	Kidney failure	635
Central nervous system	Vincristine	CYP	Nifedipine and itraconazole	Enzyme inhibition	Peripheral, autonomic, cranial nerve neuropathies and encephalopathy, neurotoxicity	636

clear whether extrahepatic metabolism provides beneficial effects by neutralizing carcinogens to which different organs of the body are exposed or if these are involved in detrimental effects by metabolic activation of procarcinogens. Continued research in this broad area will provide more answers and aid in the predictions of clinical end points.

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