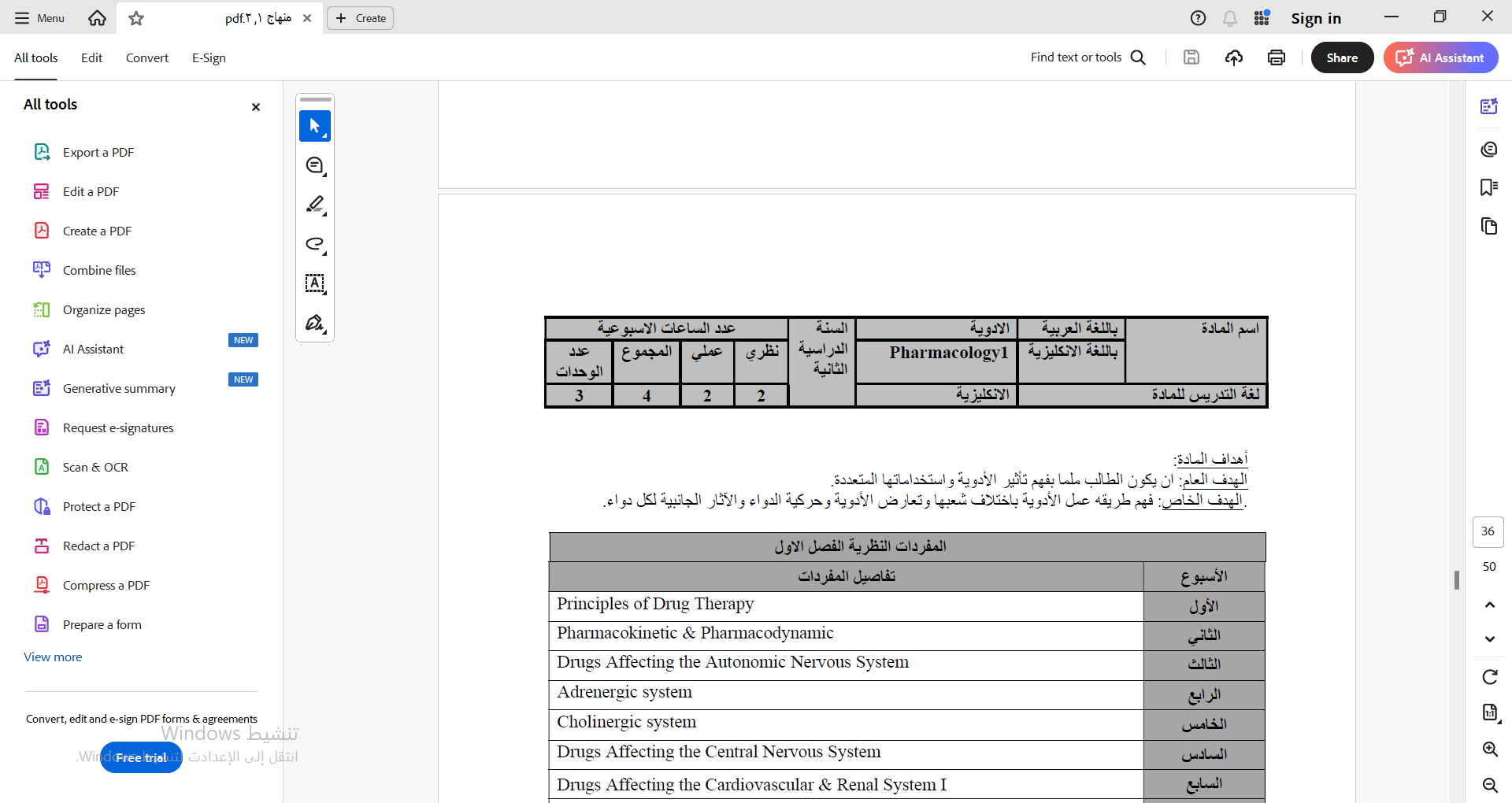
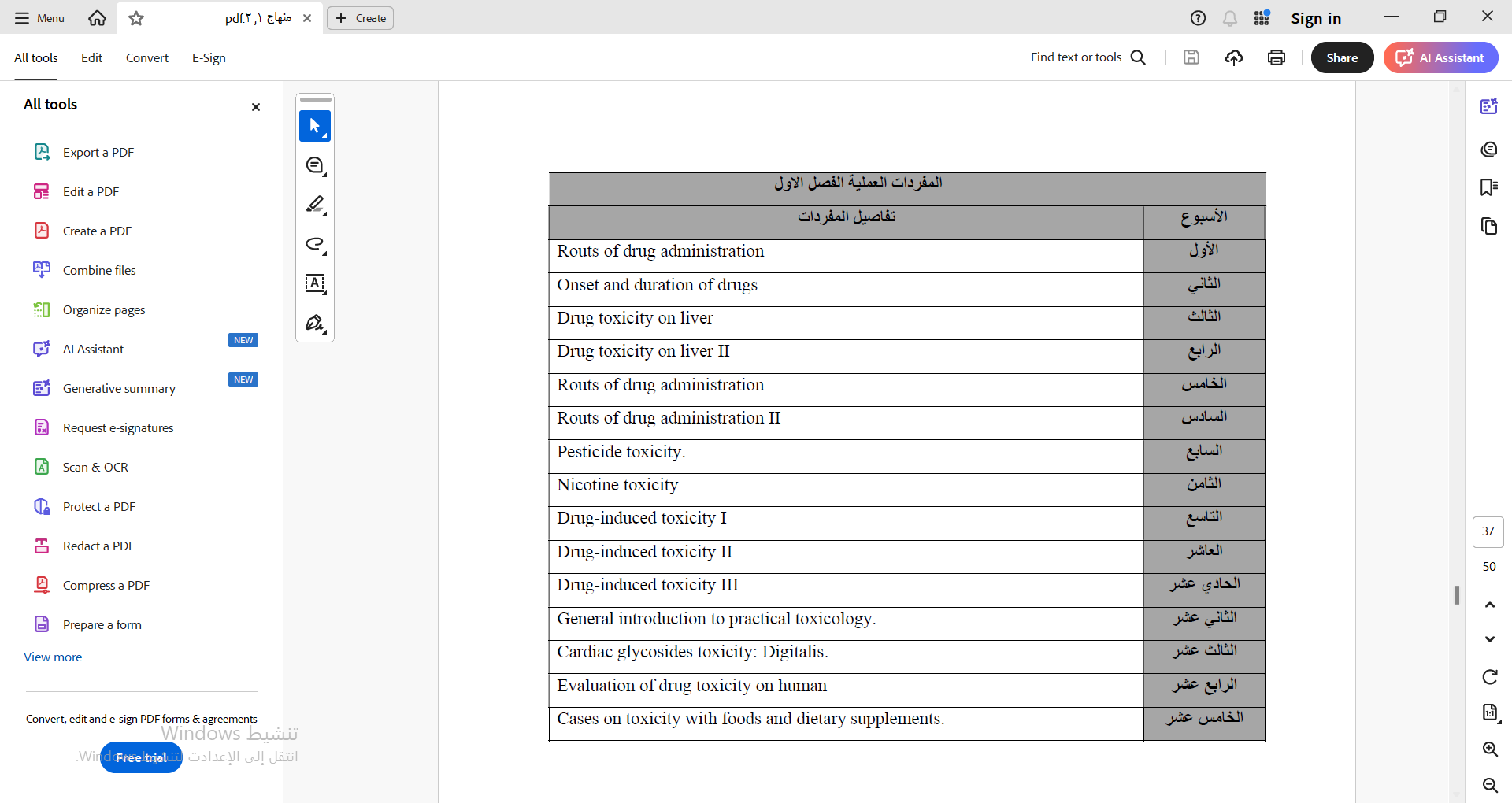
****

****

**PHARMACOLOGICAL DEFINTIONS**

**L-1**

**Drug :** a substance used in the prevention, care, or alleviation of disease or pain as an aid in some diagnostic procedures .

**Drug abuse :** an excessive or improper use of drugs, especially through self-administration for nonmedical purposes .

**Drug combinations :** the use of drugs together to enhance the properties of both to benefit of patient .

**Drug dependence :** a physical or psychological state in which a person displays withdrawal symptoms if drug use is halted suddenly, can lead to addiction .

**Drug hypersensitivity :** an allergic reaction that occurs after exposure to a suspect medication. It may manifest with a fever or rash and in severe cases, organ damage or death. It is classified as (1) immediate or occurring rapidly after exposure, or (2) delayed or occurring several days after exposure .

**Drug idiosyncrasy :** an adverse drug reaction that occurs in a small number of persons and presents to correlation to dosage or means of therapy .

**Drug interaction :** a modification of the effect of a drug when administrated with another drug .the effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug .

**Drug resistance :** the capacity of microorganism to build a tolerance to a drug .

**Drug stability :** the length of time a drug retains its properties without loss of potency usually referred to as half life .

**Drug therapy :** the use of a drug in the treatment of a patient with a specific disease or illness .

**Drug tolerance :** the body's ability to increasingly withstand the effects of the substance being used, therapy requiring larger quantities of said substance in order to bring about the desired result .

**Drug toxicity :** the critical or lethal reaction to an error dosage of a medication. Drug toxicity may occur due to human error or intentional overdose in the case of suicide or homicide .

**Drugs, antibiotic :** the chemical compounds obtained from certain living cells of lower plant forms, such as bacteria, yeasts, and molds, and form synthesis. They are antagonistic to certain pathogenic organisms and have a lethal effect on them .

**Drugs, antimicrobial :**  the drugs, mainly penicillin and its derivatives, use to combat viral, fungal and parasitic infections .

**Drugs, antiseptic :** the chemical compounds used to reduce the number of microorganisms in the oral cavity .

**Drugs, autonomic :** the drugs that mimic or block the effects of stimulation of the autonomic nervous system .

**Drugs, parasympathetic :** the belladonna alkaloids that inhibit glandular secretions of the nose, oral cavity, pharynx, and bronchi. This is main reason for using atropine and scopolamine for preanesthetic or procedure medication .

**Drugs, parasympatholytic :** the drugs that block nerve impulses passing from parasympathetic nerve fibers to postganglionic neuroeffectors, and have an effect similar to that procedure when the parasympathetic nerves are stimulated .

**Drugs, sympathetic :** the agents that imitate the sympathetic autonomic nervous system actions. They usually cause raised levels of alertness and anxiety. Various types are used in dentistry as vasoconstrictors in conjunction with local anesthetics.

**ROUTS OF DRUG ADMINISTRATION :**

**L-2**

**Choice of the route and technique of administration generally based on several factors including the :**

1. Physical properties of the drugs .
2. Formulation to be used .
3. Therapeutic indication .
4. Pathophysiologiacal of the disease .

Target species .

|  |  |  |
| --- | --- | --- |
| **Routs of Drug administration** | **advantage** | **Disadvantage** |
| **Oral (p.o.)**  Absorption after oral administration can be quite variable. Dosage form design may also be modify the rate of absorption.   * Ingestion :- * Time until effect :- 30-90 minutes | 1. Convenient (2) portable (3) safe (4) non-pain (5) easy to take (6) cheap (7) no need to sterilize but must be hygienic of course (8) compact (9) multi-dose (10) fast release tablets, capsules, enteric coated, layered tablets, slow release, suspensions, mixture . | 1. Sometimes insufficient 2. High dose or low solubility drugs may suffer poor availability only part of the dose may be absorbed . |
| **Buccal and Sublingual (S.L.)**  Ex= Nitroglycerine . | 1. First pass 2. Bioavailability is higher 3. Rapid absorption 4. Drug stability | 1. Usually more suitable for drugs with small doses 2. Drug taste may need to be masked 3. Holding the dose in the mouth is inconvenient . |
| **Rectal (P.R.)**  Drugs given by the rectal route most commonly given as suppository enema. Some drugs given by this route include; aspirin, theophylline, chlorpromazine and barbiturate | 1. By – pass liver some ( but not all ) of the veins draining the rectum lead directly to the general circulation thus by-pass liver 2. Therefore there may be reduced first-pass effect 3. Useful- for patients unable to take drugs orally or with younger children | 1. There is research being conducted to look at methods of improving the extent and variability of rectal administration 2. Absorption from solutions used as enema may be more reliable 3. Not well accepted may be some discomfort 4. Erratic absorption- drug absorption from suppository is often incomplete and erratic |
| **Intravenous (i.v.)**  Drugs given into peripheral vein over 1- 2 minutes or nlonger by infusion. Rapid injections are used to trat epileptic seizures, acute asthma or cardiac arrhythmias | 1. Rapid-quick response is possible 2. Total dose – the whole dose is delivered to the blood stream 3. Veins relatively insensitive-to irritation by irritant drugs at higher concentration in dosage forms | 1. Suitable vein-it difficult to find suitable vein 2. May be toxic 3. Requires trained personnel-trained personnel are required to give intravenous injection 4. Expensive |
| **Routs of Drug administration** | **advantage** | **Disadvantage** |
| **Subcutaneous (s/c)**  This involves administration of the drug by injection just under the skin. Commonly used for Insulin injection . | 1. Can be given by patient, e.g. in case of insulin . 2. Absorption fast from aqueous solution but more slower with depot formulations . 3. Absorption is usually complete . | 1. Can be painful 2. Drugs Finding suitable sites for repeat injection can be problem . 3. Irritant drugs cause local tissue damage 4. Maximum of 2 ml injection thus often small doses limite use |
| **Intramuscular (i.m.)** | 1. Larger volume than (s/c) can be given by (i/m) 2. They may be easier to administer than(i/v) injections 3. Depot or sustained release effect is possible with (i/m) injections e.g. procaine penicillin | 1. Trained personnel required for injection 2. The site injection with influence absorption 3. Absorption is sometimes erratic, especially for poorly soluble drugs e.g. diazepam, phenytoin 4. Irritating drug may be painful |

**Inhalation :**

1. May be used for local effect, e.g. bronchodilator .
2. Can be used for systemic effect, e.g. general anesthesia .
3. Rapid absorption by passing the liver .
4. Absorption of gases is relatively efficient .

**Topical Transdermal :**

1. Local effect – ear drops, eye drops or ointment, antiseptic creams and ointments, sunscreens, callous removal products, etc….
2. Systemic effect- e.g. nitroglycerin ointment .
3. Generally absorption is quite slow .
4. Absorption through the skin especially via cuts and absorptions or form sites were the skin is quite thin can be quite marked .

**Transdermal :**

Transdermal patches can provide prolonged or controlled drug delivery .

1. There may be some skin irritation .
2. Drug absorption will vary by site of administration, skin condition, age and gender
3. Systemic absorption (transdermal) is better with low doses, lipid soluble drugs .

**Other routes :**

1. Nasal .
2. Intra-arterial –for cancer chemotherapy to maximize drug concentration at the tumor site .
3. Intrathecal directly into the cerebrospinal fluid .
4. Topical, ocular, aural, vaginal .

**Routs for administration of drugs and time until effect**

|  |  |
| --- | --- |
| **Routs for drugs administration** | **Time until effect** |
| Intravenous | 30-60 second |
| Intraosseeous | 30-60 second |
| Endotracheal | 2-3 minutes |
| Inhalation | 2-3 minutes |
| Sublingual | 2-5 minutes |
| Intramuscular | 10-20 minutes |
| Subcutaneous | 15-30 minutes |
| Rectal | 5-30 minutes |
| Ingestion | 30-90 minutes |
| Transdermal | Variable (minutes to hours) |

**DRUG TOXICITY ON LIVER**

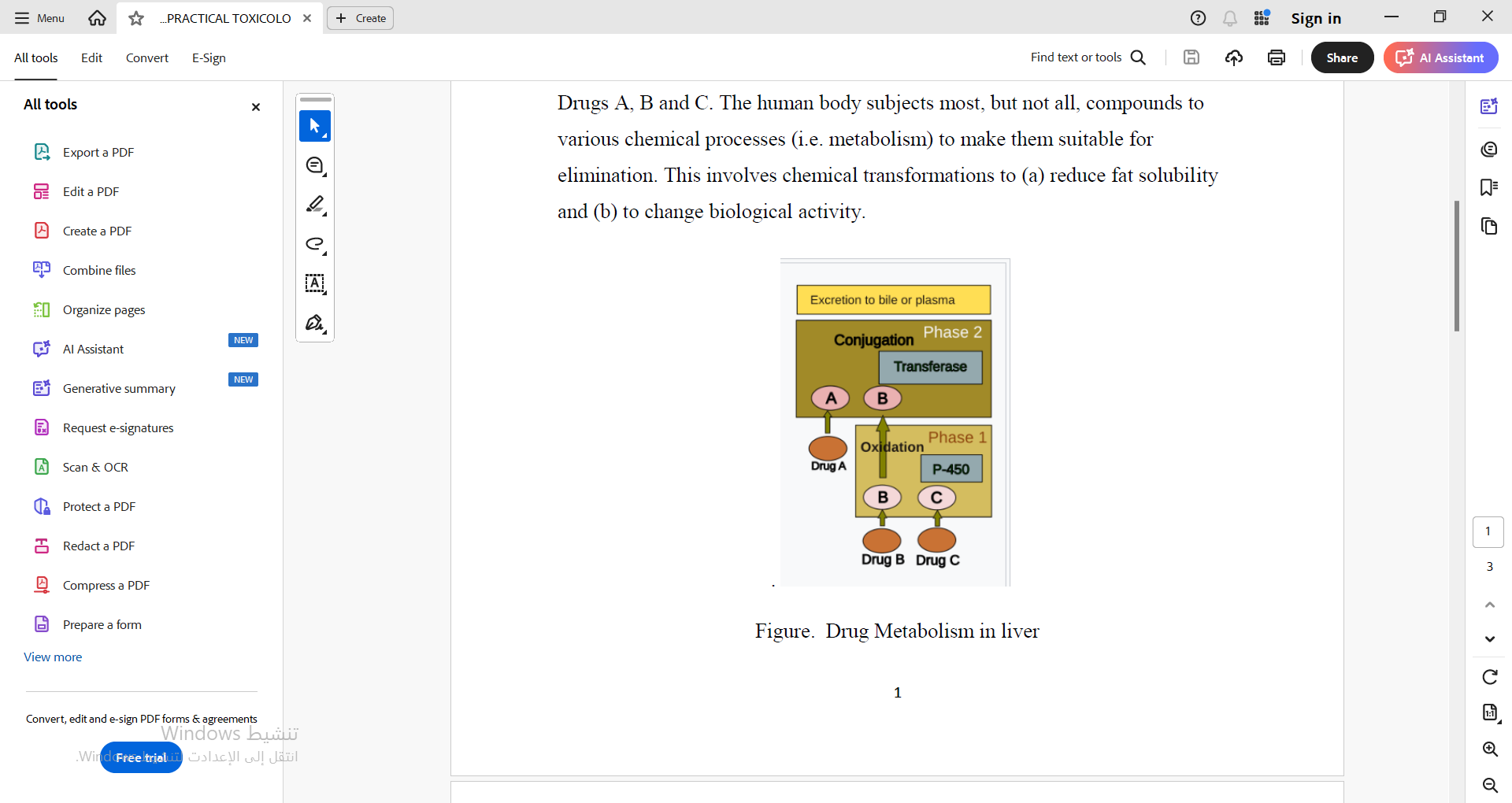
**L-3**

**Drug-induced liver injury (DILI)** is a cause of acute and chronic liver disease caused specifically by medications and the most common reason for a drug to be withdrawn from the market after approval.

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses (e.g. acetaminophen, paracetamol) and sometimes even when introduced within therapeutic ranges (e.g. halothane), may injure the organ.

* **Drug metabolism in liver**

Drug metabolism in liver: transferases are: glutathione, sulfate, acetate, glucoronic acid. P-450 is cytochrome P-450. Different pathways are shown for Drugs A, B and C. The human body subjects most, but not all, compounds to various chemical processes (i.e. metabolism) to make them suitable for elimination. This involves chemical transformations to (a) reduce fat solubility and (b) to change biological activity(fig. 2).

 **Figure 2**. Drug Metabolism in liver.

Drug metabolism is usually divided into two phases: phase 1 and phase 2. Phase 1 reaction is generally speaking to prepare a drug for phase 2. However, many compounds can be metabolized by phase 2 directly or be excreted without any phase 2 reactions occurring. Phase 1 reaction involves oxidation, reduction, hydrolysis, hydration and many other rare chemical reactions. These processes tend to increase water solubility of the drug and can generate metabolites that are more chemically active and/or potentially toxic. Most of phase 2 reactions take place in cytosol and involve conjugation with endogenous compounds via transferase enzymes. Phase 1 are typically more suitable for elimination.

* **Paracetamol**

Paracetamol also known as acetaminophen, and by the brand names of Tylenol and Panadol, is usually well-tolerated in prescribed dose, but overdose is the most common cause of drug-induced liver disease and acute liver failure worldwide. Damage to the liver is not due to the drug itself but to a toxic metabolite (N-acetyl-p-benzoquinone imine (NAPQI)) produced by cytochrome P-450 enzymes in the liver. In normal circumstances, this metabolite is detoxified by conjugating with glutathione in phase 2 reaction. In an overdose, a large amount of NAPQI is generated, which overwhelms the detoxification process and leads to liver cell damage. Nitric oxide also plays a role in inducing toxicity.

* **Nonsteroidal anti-inflammatory drugs**

Although individual analgesics rarely induce liver damage due to their widespread use, NSAIDs have emerged as a major group of drugs exhibiting hepatotoxicity. Both dose-dependent and idiosyncratic reactions have been documented. Aspirin and phenylbutazone are associated with intrinsic hepatotoxicity; idiosyncratic reaction has been associated with ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac and indomethacin. **LECTURE**

* **Glucocorticoids**

Glucocorticoids are so named due to their effect on the carbohydrate mechanism. They promote glycogen storage in the liver. An enlarged liver is a rare side-effect of long-term steroid use in children. The classical effect of prolonged use both in adult and paediatric population is steatosis.

* **Isoniazid**

Isoniazide (INH) is one of the most commonly used drugs for tuberculosis; it is associated with mild elevation of liver enzymes in up to 20% of patients and severe hepatotoxicity in 1-2% of patients.

**Nicotine toxicity**

**L-4**

Nicotine is one of the most widely abused chemical and now considered to be one of the most addicting substances. It is the principal pharmacologically active component of tobacco in which poisoning may occur in accidental ingestions of tobacco products (especially by children), use of nicotine-containing gums, and industrial exposure to tobacco products, contact with some pesticides and so on. Nicotine has both stimulant and depressant action. Nicotine is readily absorbed through intact skin as well as through mucus membranes and the respiratory tract. It is metabolized by the liver and excreted by the kidney. Victims can complain of nausea, emesis, excessive salivation, and diarrhea at low doses. But at high dose it can cause respiratory paralysis, cardiovascular collapse, and convulsions.

There is no simple qualitative test for Nicotine, but this compound can be detected and identified by thin layer chromatography of a basic solvent extract of urine.

**Laboratory analysis**

**General test**

CBC (polymorph nuclear leukocytosis), electrolytes, BUN, creatinine, arterial blood-gas analysis, liver function tests, urine nalysis (Glycosuria)

**Toxin specific tests**

- **Serum nicotine levels** should be determined as early as possible, but the short half-life of nicotine makes it difficult to accurately assess the level of int**o**xication.

**- Urine nicotine levels** – are inconsistent owing to the altered excretion of nicotine with changes in urine pH. They may be useful as a guide to the level of chronic

exposures.

**L-5**

**DRUG TOXICITY**

**TOXICITY OF ANTIBIOTICS**

**ANTIBIOTIC**

An **antibiotic** is a type of [antimicrobial](https://en.wikipedia.org/wiki/Antimicrobial) substance active against [bacteria](https://en.wikipedia.org/wiki/Bacteria). It is the most important type of antibacterial agent for fighting [bacterial infections](https://en.wikipedia.org/wiki/Pathogenic_bacteria), and antibiotic [medications](https://en.wikipedia.org/wiki/Medication) are widely used in the [treatment](https://en.wikipedia.org/wiki/Therapy) and [prevention](https://en.wikipedia.org/wiki/Antibiotic_prophylaxis) of such infections. They may either [kill](https://en.wikipedia.org/wiki/Bactericide) or [inhibit the growth](https://en.wikipedia.org/wiki/Bacteriostatic_agent) of bacteria. A limited number of antibiotics also possess [antiprotozoal](https://en.wikipedia.org/wiki/Antiprotozoal) activity. Antibiotics are not effective against [viruses](https://en.wikipedia.org/wiki/Virus) such as the ones which cause the [common cold](https://en.wikipedia.org/wiki/Common_cold) or [influenza](https://en.wikipedia.org/wiki/Influenza).[[5]](https://en.wikipedia.org/wiki/Antibiotic#cite_note-5) Drugs which inhibit growth of viruses are termed [antiviral drugs](https://en.wikipedia.org/wiki/Antiviral_drug) or antivirals. Antibiotics are also not effective against [fungi](https://en.wikipedia.org/wiki/Fungi). Drugs which inhibit growth of fungi are called [antifungal drugs](https://en.wikipedia.org/wiki/Antifungal_drug).

**Side effects**

Health advocacy messages such as this one encourage patients to talk with their doctor about safety in using antibiotics.

Antibiotics are screened for any negative effects before their approval for clinical use, and are usually considered safe and well tolerated. However, some antibiotics have been associated with a wide extent of adverse [side effects](https://en.wikipedia.org/wiki/Side_effect) ranging from mild to very severe depending on the type of antibiotic used, the microbes targeted, and the individual patient. Side effects may reflect the pharmacological or toxicological properties of the antibiotic or may involve hypersensitivity or [allergic](https://en.wikipedia.org/wiki/Allergy) reactions(fig.3 ). Adverse effects range from fever and nausea to major allergic reactions, including [photodermatitis](https://en.wikipedia.org/wiki/Photodermatitis)(fig. 4) and [anaphylaxis](https://en.wikipedia.org/wiki/Anaphylaxis).





Figure 3 . Allergic reaction. Figure 4 . [Photodermatitis](https://en.wikipedia.org/wiki/Photodermatitis)

Common side effects of oral antibiotics include [diarrhea](https://en.wikipedia.org/wiki/Diarrhea), resulting from disruption of the species composition in the [intestinal flora](https://en.wikipedia.org/wiki/Intestinal_flora), resulting, for example, in overgrowth of pathogenic bacteria, such as [*Clostridioides difficile*](https://en.wikipedia.org/wiki/Clostridioides_difficile_(bacteria)). Taking [probiotics](https://en.wikipedia.org/wiki/Probiotics) during the course of antibiotic treatment can help prevent antibiotic-associated diarrhea. Antibacterials can also affect the [vaginal flora](https://en.wikipedia.org/wiki/Vaginal_flora), and may lead to overgrowth of [yeast](https://en.wikipedia.org/wiki/Yeast) species of the genus [*Candida*](https://en.wikipedia.org/wiki/Candida_(genus)) in the vulvo-vaginal area.[[50]](https://en.wikipedia.org/wiki/Antibiotic#cite_note-Pirotta_and_Garland-50) Additional side effects can result from [interaction](https://en.wikipedia.org/wiki/Drug_interaction) with other drugs, such as the possibility of [tendon](https://en.wikipedia.org/wiki/Tendon) damage from the administration of a [quinolone antibiotic](https://en.wikipedia.org/wiki/Quinolone_antibiotic) with a systemic [corticosteroid](https://en.wikipedia.org/wiki/Corticosteroid). Some antibiotics may also damage the [mitochondrion](https://en.wikipedia.org/wiki/Mitochondrion), a bacteria-derived organelle found in eukaryotic, including human, cells.[[52]](https://en.wikipedia.org/wiki/Antibiotic#cite_note-52) Mitochondrial damage cause [oxidative stress](https://en.wikipedia.org/wiki/Oxidative_stress) in cells and has been suggested as a mechanism for side effects from [fluoroquinolones](https://en.wikipedia.org/wiki/Fluoroquinolone). They are also known to affect [chloroplasts](https://en.wikipedia.org/wiki/Chloroplast).

**DRUGS OF ABUSE**

 All drugs are toxic at some dose. Drugs of abuse, however, either have no medicinal function or are taken at dose levels higher than would be required for therapy. Although some drugs of abuse may affect only higher nervous functions—mood, reaction time, and coordination—many produce physical dependence and have serious physical effects, with fatal overdoses being a frequent  **Figure 5**. Drug abuse

occurrence. The drugs of abuse include central nervous system depressants such as ethanol, methaqualone (Quaalude), and secobarbital; central nervous system stimulants, such as cocaine, methamphetamine (speed), caffeine, and nicotine; opioids, such as heroin and mependine (demerol); and hallucinogens such as lysergic acid diethylamide (LSD) phencyclidine (PCP), and tetrahydrocannabinol, the most active principal of marijuana. A further complication of toxicological significance is that many drugs of abuse are synthesized in illegal and poorly equipped laboratories with little or no quality control. The resultant products are therefore often contaminated with compounds of unknown,, but conceivably dangerous, toxicity(fig. 5).

**GENERAL INTRODUCTION TO PRACTICAL TOXICOLOGY**

**L-6**

* **Toxicology** is one of the oldest branches of pharmacology, and was once called or Toxicology knows poisons. Definition of Toxicology the definition of toxicology includes metabolism Excretion and method of action of these toxins Poisoning treatment.
* **Toxicology** is defined as the study of the adverse effects of chemicals on living organisms. The term toxicity is defined as the inherent capacity of a chemical to cause injury. Thus, all chemicals, including drugs, have some degree of toxicity.
* Toxicokinetic and toxicodynamic are two fundamental concepts in the field of toxicology.
* Toxicokinetic: They describe the processes by which toxic substances distributed, are absorbed, metabolized, eliminated in the body.
* Toxicokineticrefers to the study of the movement of toxic substances within the body. ◦Thisincludestheabsorption, distribution, metabolism, and excretion (ADME)of the toxicants.
* Toxicodynamic: They also describe how these substances exert their effects on target cells, tissues and Toxicodynamic involves understanding the mechanisms of action, dose response relationships, and factors influencing individual susceptibility to toxicity. organs.
* **Toxicity:** Toxicity is defined as the ability of a substance to cause harm to a living organism, and it is an estimated value expressed as the amount of poison per unit weight of the organism being treated with it.
* **Poison:** Poison was defined by orfila in 1821. any substance that enters the body of a living organism in any way and in a dose very small, causing a harmful effect on health or leading to totally dead.
* **Toxin:** A toxin is a toxic substance produced naturally by living organisms.
* **Toxicant:** A toxicant or poison is meant to be a toxic substance produced naturally or prepared by man.
* **Venom:** The expression venom means that it is the poison that is produced by the animal to be poisoned by it the degree of particularity other types of animals by means of a special mechanism designed to give venom.
* **Dose:** is the amount of the actual chemical compound that enters the body of the organism and expresses it milligrams of compound/kg of body weight(mg/kg
* **Dosage:** It is the amount of the chemical compound per unit weight of the exposed individual per day mg(dose)/kg(b.w.)/day.
* **LD50(LethalDose50):** It is the dose of a single substance that causes 50% of the population of living organisms (animals) to die as a result exposure to this substance by any method of exposure other than through breathing.
* **Less lethal dose low (LD**LO**):** LDLO is defined as the lowest dose of a substance which enters the body by any means of entry except through breathing, which causes death in human and animals.

CARDIAC GLYCOSIDES TOXICITY: DIGITALIS.

**L-7**

**Introduction:**

* Cardiac glycosides represent a family of compounds that are derived from the foxglove plant (Digitalis purpurea)(fig.6 ). The therapeutic benefits of digitalis were first described by William Withering in 1785. Initially, digitalis was used to treat dropsy, which is an old term for edema.



**Figure 6.** The foxglove plant (Digitalis purpurea)

* Digitalis glycosides are life-saving drugs when used in therapeutic doses in the treatment of congestive heart failure (CHF), & for management of certain supraventricular arrhythmia.
* Digoxin is the one of the most widely prescribed drugs
* Digoxin acts through inhibition of the Na+/K+ adenosine triphosphatase (ATPase) enzyme as shown in Figure 7 .

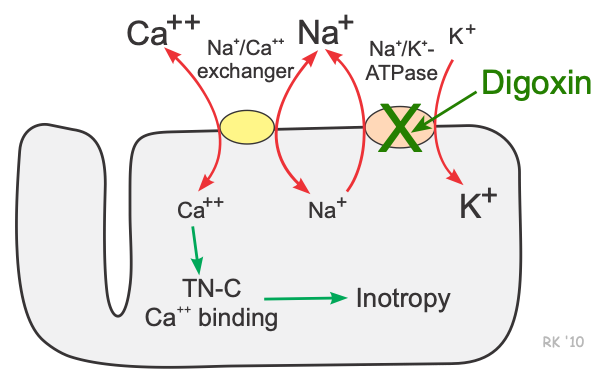


Figure 7. Mechanism of action of cardiac glycosides, or digitalis. ATPase =

adenosine triphosphatase.

▪ It is estimated that 20-30% of patients taking a digitalis preparation will experience toxicity because the drugs have an extremely narrow therapeutic index.

▪ The serum concentration of digoxin for therapeutic activity is in the normal range of 1.2-1.7 ng/mL & clinically significant toxicity usually occurs with concentrations 2-3 times higher.

▪ The mortality rate with toxic dose is reported to be as great as 25%.

**Factors that increase the risk of toxicity to**

Digitalis glycosides:

▪ Concurrent administration of a diuretic that induces potassium loss is reported to be the most frequent cause of toxicity.

▪ Individuals with Eubacterium lentum in their colon may require larger doses of digitalis to achieve the desired therapeutic serum concentrations.

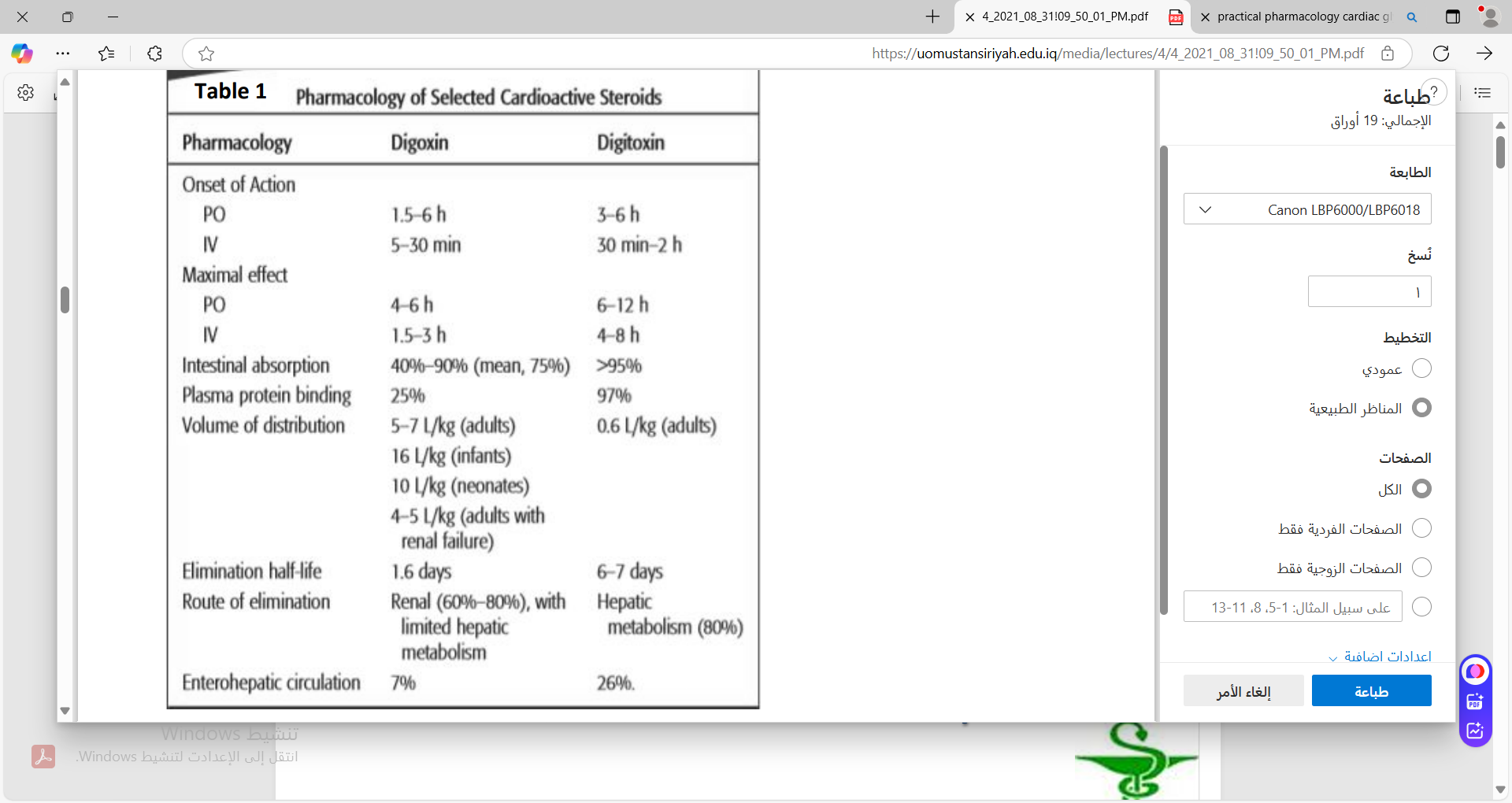
▪ Since 60-80% of digoxin is excreted through the kidneys as shown in Table 1, decreased renal excretion would result in accumulation of digoxin & toxicity.

▪ Interactions with other drugs such as verapamil & quinidine (they cause increase in plasma concentration of digoxin probably by digoxin displacement from tissue-binding sites)

▪ Hypokalemia, &

▪ Hypothyroidism.

Table 4.Pharmacology of selected cardiovascular steroids.



**Characteristics of poisoning:**

▪ Early manifestations of intoxication that occur in approximately 50% of all cases generally involve the gastrointestinal tract:

Anorexia, nausea, vomiting, & abdominal pain are common.

Nausea & vomiting occur from direct drug action on the chemoreceptor trigger zone (CTZ(

▪ Blurred vision, loss of visual acuity, & green yellow halos have been described as early-appearing symptoms.

▪ CNS effects include a variety of neuropsychiatric disturbances.

▪ Digitalis intoxication can provoke a large number of arrhythmias. These include bradyarrhythmias or tachyarrhythmias, or a combination of both.

**Management of poisoning:**

▪ Management of acute digitalis toxicity involves removal of ingested drug, maintenance of a normal potassium concentration, reversal of arrhythmias, & the use of a specific antidote (digoxin immune Fab).

▪ Gastric lavage should be performed to remove the unabsorbed drug, although vomiting may already have accomplished this.

▪ Repeated administration of activated charcoal or cholestyramine is recommended to enhance elimination of the glycoside by interrupting to entero-hepatic cycling exhibited by digitoxin, & possibly digoxin.

▪ Hyperkalemia (5.5-13.5 mEq/L) is caused by acute digitalis toxicity, while hypokalemia is more common with chronic digitalis use.

▪ Hyperkalemia may require treatment with insulin plus glucose, & sodium bicarbonate.

▪ If hypokalemia is encountered with tachy- or bradyarrhythmias, continuous potassium replacement alone may be sufficient.

▪ For atrial & ventricular arrhythmias that do not respond to potassium therapy, the treatment of choice includes phenytoin & lidocaine.

▪ Potassium administration in a person with digitalisinduced hyperkalemia can result in heart block.

▪ If digitalis has produced atrioventricular (AV) block, atropine is given to produce vagolytic effect to increase the heart rate & AV conduction.

▪ β-blockers, such as propranolol, are useful to suppress supraventricular & ventricular arrhythmias but may depress the sinoatrial (SA) node & AV conduction especially in a patient with an already failing heart, that limiting their usefulness.

▪ Because digoxin has a large volume of distribution, hemodialysis is not a successful method to enhance elimination of digoxin. However, hemodialysis is still sometimes required…..why?

**Digoxin Immune Fab (Digibind:(**

❖ Digoxin immune Fab is used as an antidote reserved for life-threatening overdoses.

❖ Indications of such toxicity include:

• ingestion of more than 10 mgof digoxin by healthy adults or 4 mg by children,

• Steady-state serumconcentrations greater than 10 ng/mL; or

• if blood potassium concentration exceeds 5 mEq/L.

❖ Dosage of digibind can be calculated according to the amount of digoxin or digitoxin in the patient’s body.

❖ When steady-state serum concentrations of digoxin or digitoxin is known, the total body load can be estimated as shown below:

**Body load(mg)= (SDC)(mean Vd)(wt in Kg)/ 1000**

SDC is the serum digitalis concentration in ng/mL.

Vd: volume of distribution

Vd of digoxin = 5.6 L/kg

Vd of digitoxin = 0.56 L/kg

❖ Each vial of antidote contains 40 mg of digibind. This will bind 0.6 mg digoxin or digitoxin.

❖ The total number of vials needed can be obtained by

dividing the total body load of drug in mg, by 0.6 mg/vial.

❖ Adverse effects to digibind have been minimal including

sensitivity, erythema at the site of injection, rash & urticaria have been reported.

Q/ How many milligrams & vials of digoxin-specific antibody fragment are required to treat a 40 years old male patient, weighing 70 kg in whom digoxin assay revealed a steady state serum concentration of 0.015 μg/mL?

Body load(mg)= (SDC)(mean Vd)(wt in Kg)/1000

Serum digitalis concentration in ng/mL= 15

Vd of digoxin = 5.6 L/kg

Body load= 15 x 5.6 x 70/1000= 5.88 mg of digoxin.

Each vial of digibind contains 40 mg

40 mg of digibind would bind 0.6 mg of digoxin

40 mg (digibind) x (digibind(

0.6 mg (digoxin) 5.88 mg

X = 392 mg of digibind

392 mg/ 40 mg/vial= 9.8 which means 10 vials

EVALUATION OF DRUG TOXICITY ON HUMAN

**L-8**

Introduction

As healthcare professionals, we often encounter situations where toxicology testing becomes a critical part of a patient’s care. Whether it’s determining the presence of illicit drugs, checking for prescription medication compliance, or ruling out exposure to harmful substances, it provides key insights that guide our treatment decisions. But many patients and even healthcare providers are not fully familiar with how these tests work, what they can detect, and why they are so important.

* **What is Toxicology testing in Healthcare?**

Toxicology testing refers to the analysis of biological samples (like urine, blood, or hair) to detect the presence of harmful substances. These tests can detect drugs, alcohol, heavy metals, toxins, and other chemicals. They range from simple tests to more detailed lab analyses, depending on what’s being checked. It helps doctors understand a patient’s health, find the cause of symptoms, track medication use, or confirm if harmful substances were involved.

* **What are the different types of Toxicology tests?**

It is not one-size-fits-all. Different types of tests are used depending on the circumstances, the substances involved, and the urgency of the situation.

Below are the main types of toxicology tests and their specific uses:

* **Urine tests**

What it detects: Urine tests are typically used to detect substances that have been used within the past few days. Drugs such as cocaine, marijuana, opioids, amphetamines, and benzodiazepines can be detected in urine. Alcohol can also be detected, but its presence usually fades more quickly than other substances.

**Advantages:**

* Inexpensive and provide quick results.
* Able to screen for a wide variety of substances.

**Limitations:**

* Detect substances currently present in the body, but not long-term use or history.
* Some substances may be excreted too quickly to be detected

.

* **Blood Tests**

What it detects: Blood tests are often used to detect substances such as alcohol, prescription drugs, and drugs of abuse, particularly when a patient is experiencing an acute reaction. This type of testing is especially useful in monitoring drug overdoses, toxic exposures, and medication levels.

**Advantages:**

* Provide precise information about the concentration of a substance in the bloodstream.
* Essential for diagnosing and managing poisoning or overdose cases.

**Limitations:**

* Require professional medical personnel for collection and are more expensive.
* Cannot detect substances already metabolized and removed from the body.
* **Hair tests**

What it detects: Hair tests can detect a history of drug use over weeks or even months. This makes hair testing useful in forensic investigations, child custody cases, or monitoring substance abuse treatment progress. Substances such as cocaine, marijuana, and opioids can be detected in hair.

**Advantages:**

* Offer a longer window of detection compared to urine or blood tests.
* Useful in confirming long-term or repeated exposure to drugs or toxins.

**Limitations:**

* Not useful for detecting recent drug use (within the past few days).
* Hair sample collection may be more invasive and less widely available.
* Saliva and sweat tests

**What it detects:**

* Saliva tests detect drugs used within the past few hours.
* Sweat tests monitor ongoing drug use over days or weeks.

**Advantages:**

* Saliva tests are non-invasive, easy to collect, and provide rapid results.
* Sweat tests enable continuous monitoring over a long period.

**Limitations:**

* Shorter detection window compared to urine or blood tests.
* Less commonly used and may not detect all substances.
* **Environmental and occupational testing**

What it detects: This form of testing can detect heavy metals, pesticides, solvents, and other industrial chemicals that may accumulate in the body over time.

**Advantages:**

* Provides essential information for workplace safety management.
* Helps prevent long-term exposure to toxic substances.

**Limitations:**

* May require specialized methods and equipment.
* Not as readily available as standard drug tests and may not effectively detect acute exposure.

**How does Toxicology testing work?**

The testing works by detecting specific substances in the body’s biological samples.The process typically involves the following steps:

* **Collection:** The first step is collecting the sample, whether it’s urine, blood, hair, or another biological substance. The sample must be collected properly to ensure accurate results. For example, in urine testing, the patient is usually asked to provide a “midstream” sample, which helps avoid contamination from substances present in the urethra. For blood tests, the sample is drawn using a sterile needle, and for hair tests, a small section of hair is cut near the scalp.
* **Screening:** Once the sample is collected, it undergoes an initial screening. This step typically involves using immunoassay techniques, which are designed to quickly identify the presence of specific substances. If a substance is detected, the sample may undergo confirmation testing to ensure accuracy. Screening tests are generally quick and cost-effective but may have limitations in specificity, meaning false positives can occur.
* **Confirmation:** If the screening results indicate the presence of a potential substance, more specific and accurate tests are used to confirm the findings. These tests, such as gas chromatography-mass spectrometry (GC-MS), provide precise identification of substances and their concentrations. This confirmation step is critical for ruling out false positives and ensuring that the test results are reliable.
* **Interpretation:** After confirmation, the results are analyzed by a toxicologist or laboratory specialist. They assess the levels of substances detected and interpret their significance in relation to the patient’s health. The results are then sent to the healthcare provider, who can use them to make informed decisions about diagnosis and treatment. This interpretation often requires considering the timing of exposure, the patient’s clinical symptoms, and their medical history

.

* **What does Toxicology testing detect?**

These are designed to detect a wide range of substances that can negatively impact health.

**These include:**

* **Drugs and Alcohol:** One of the most common uses of testing is to detect the presence of illicit drugs or alcohol. This includes substances such as cocaine, marijuana, opioids, amphetamines, and alcohol. For patients with suspected substance abuse issues, it helps confirm or rule out drug use, guiding treatment options. Detection can vary based on the drug’s half-life and the type of test used (urine, blood, hair, etc).
* **Prescription Medications:** It can also identify prescription drugs that are being taken, either to ensure that a patient is adhering to their prescribed regimen or to detect potential misuse or overdose. Testing for drugs like opioids, benzodiazepines, and stimulants can help prevent dangerous drug interactions or misuse. Misuse of prescription medication is a growing concern, making testing a vital tool for managing patients on long-term medication therapy.
* **Heavy Metals:** Exposure to heavy metals like lead, mercury, and arsenic can have serious health consequences, especially in children. It can detect the presence of these metals in the body and help healthcare providers address potential poisoning. Testing for heavy metals is particularly important for individuals working in certain industries or living in areas with environmental contamination.
* **Environmental Toxins:** Toxicology tests can identify exposure to chemicals in the environment, such as pesticides, herbicides, and industrial chemicals. This is particularly important for individuals who live in areas with high pollution levels or work in industries where exposure to harmful chemicals is a concern. Monitoring for environmental toxins helps prevent long-term health problems related to chronic exposure.
* **Over-the-Counter Medications and Supplements:** Some tests can detect over-the-counter medications and dietary supplements, which might cause unintended side effects or interactions when taken with other substances. Patients often forget to mention OTC drugs or supplements, which is why toxicology test is essential for understanding all possible factors affecting a patient’s health.
* **Why Is Toxicology testing important?**

It plays an essential role in patient care for several reasons:

* **Early Detection of Harmful Substances:** It helps identify potentially dangerous substances in the body early, allowing healthcare providers to intervene quickly and prevent further harm. This is particularly important in cases of poisoning or overdose, where time is critical.
* **Accurate Diagnosis:** Many health conditions, such as drug overdoses, poisoning, and withdrawal symptoms, can be mistaken for other illnesses. It provides concrete evidence of what is affecting the patient, leading to more accurate diagnoses.
* Patient Safety: By monitoring medication use and detecting potential drug interactions, it helps ensure that patients are taking their medications safely and as prescribed. It also helps avoid dangerous drug combinations that could cause harm.
* **Workplace and Legal Concerns:** It is often used in workplaces to screen for drug use, and it can also play a role in legal cases involving substance abuse or poisoning. Law enforcement and legal teams rely on toxicology results to help investigate suspected drug use or poisoning incidents.

Practical tips for patients and healthcare providers

**Here are some practical tips to ensure that toxicology testing is used effectively:**

* **For patients**
* **Be honest about your health history:** Always inform your healthcare provider about any medications (prescription or over-the-counter) you are taking, as well as any illicit drug use. This information helps ensure accurate test results and appropriate treatment.
* **Understand the testing process:** Ask your healthcare provider to explain why a toxicology test is necessary, how it will be done, and what substances will be tested. Understanding the process can reduce anxiety and improve cooperation.
* **Follow test instructions:** When asked to provide a sample for testing, be sure to follow the instructions carefully. For example, avoid contaminating urine samples with outside substances or drinks that might interfere with the test results.
* **For healthcare providers**
* **Use testing appropriately:** Toxicology tests are a powerful tool, but they should be used appropriately. Make sure to select the right type of test based on the patient’s symptoms, history, and suspected exposure.
* **Interpret results carefully:** Toxicology results must be interpreted in the context of the patient’s health status. Elevated levels of a substance may be harmless in some contexts, while in others, they could signal a serious issue. Be mindful of possible false positives or false negatives.
* **Advocate for patient education:** Educate your patients on the importance of toxicology testing, especially when they are prescribed new medications. Help them understand how certain substances might interact with others and the importance of following instructions.

CASES ON TOXICITY WITH FOODS AND DIETARY SUPPLEMENTS

* **FOOD AND TOXICITY:**

Food toxicant can be divided into three categories, namely endogenous, naturally

occurring and synthetic.

1. Endogenous toxicants:

 Substances produced by tissue cells in plants and other biological raw

materials.

 Chemical substances often serve the purpose of protecting plant tissues from

pests, as well as from pathogenic organism.

 Transmission to man can be direct consumption of toxic plants or from

animals who have consumed the plant that are used for human foods.

 Examples include flavonoids, cyanogenic compounds, and mushroom

toxins.

 Toxicological effects range from acute effects of gastroenteritis to more

severe toxicities in the CNS leading to death.

2. Synthetic toxicants:

 Synthetically produced.

 Found their way into food supply through contamination of the food

processing environment e.g pesticides, additives, preservatives.

 Pesticides include insecticides, herbicides, rodenticides, fungicides, etc.

 Amide herbicides (propanil) which is used extensively to control harmful

weeds in rice crops could cause liver damage, CNS depression and death.

3. Naturally occurring toxicants.

 They are produced by organism that contaminate the food products.

 Microorganism such as fungi, and bacteria can produce toxicants that upon

consumption can cause diseases.

* **Risks of toxins in food**

• Carcinogenic

• Mutagenic

• Teratogenic

• Endocrine disrupters (hormones)

• Microbial pathogens

* **Endogenous Toxins of Plant Origin**

 Flavonoids

 A class of plant pigments that are widely present in human food, are the flavonoids

 Sources of flavonoids include: apples, apricots, blueberries, raspberries, strawberries

 At low concentrations  the effects of flavonoids are thought to be potentially anticarcinogenic because flavonoids can block and inhibit the excessive cell division characterized by cancer.

 High concentrations of flavonoids may promote cancer formation → can damage the chromosomes and DNA in cells, leaving them more susceptible

to cancer.

 Can interfere with the metabolism of drugs and with mineral absorption in

Body.

 Daily intake: 150-250 mg/day

 Tannins

 Tannins are a heterogeneous group of broadly distributed substances of plant origin.

 Source of Tannins

Fruits, tea (highest content), coffee, cocoa, grape, wine.

 Toxicity: cause acute liver injury, i.e., liver necrosis and fatty liver.

 If ingested in excessive quantities→ inhibit the absorption of minerals such as iron → lead to anemia

 In sensitive individuals, a large intake of tannins may cause bowel irritation,

kidney irritation, liver damage, irritation of the stomach and gastrointestinal pain.

 Cyanogenic glycosides

 Sources: lima beans, peas, bitter almonds

 Cyanogenic glycoside is not toxic on its own.

 When fresh plant material is damaged by chewing, cutting, insect attack→ it

will be subsequently broken down to sugar and a cyanohydrin which rapidly decomposes to an aldehyde or a ketone and releases the toxic hydrogen

cyanide.

 Toxic cyanide is released when the plant is cut into small pieces during food

preparation, and the resulting hydrogen cyanide is easily removed by cooking in water since its volatile.

 It can be fatal if those food are eaten raw or prepared improperly.

 Peeling, washing in running water and cooking or fermenting can remove

and volatilize the cyanide.

 Acute and chronic biochemical effects in biological system: inhibition of the

antioxidant defense, alteration of cellular ion homeostatis and inhibition cellular respiration

 Symptoms: mental confusion, muscular paralysis, respiratory distress.

 Glucosinolates

 Substances that can be considered as natural toxins, but also as antinutritives

 Source: cabbage and turnips.

 Toxicity: cytotoxic and mutagenic.

 Mushroom toxins

 Caused by the high content of amatoxins in mushrooms.

 There are four categories of mushroom toxins:

1. Neurotoxins

Cause neurological symptoms such as profuse sweating, hallucinations, depression, spastic colon, excitement, convulsions, and coma.

**2. Protoplasmic poisons**

Cause generalized destruction of cells, which is followed by organ failure.

**3. Gastrointestinal irritants**

Produce rapid, transient nausea, abdominal cramping, vomiting, and diarrhea.

**4. Disulfram-like toxins**

Disulfram-like toxins are usually nontoxic and produce no symptoms. However, if alcohol is consumed within 72 hours after eating them, they may produce vomiting, nausea, headache, flushing, and cardiovascular disturbances.

 The first symptoms of mushroom poisoning occur within 6-24 hr. after ingestion of the mushroom(phase one)

 Phase two, also called the gastrointestinal phase, involves sever vomiting, abdominal cramps, nausea, and diarrhea.

 Phase three lasts about 12-24 hr. and is characterized by improved

clinical symptoms; however, it is also the beginning of liver necrosis.

 Phase four (the last phase), result in hepatic failure, encephalopathy, internal bleeding, and acute renal failure.

 Patients usually die within 5-20 days after ingestion of the mushrooms.

* **Natural Contaminants**

There are three important sources:

 Raw materials of plant origin can become contaminated if they are

mixed with toxic non-nutritive plant species.

 Raw materials of animal origin, mainly fish and milk, can also become contaminated if the animal has ingested toxic substances of natural origin.

 Contaminants of natural origin can be the products of microorganisms.

Microbial Toxin: Mycotoxin

 Mycotoxins are secondary metabolites of fungi which can induce acute as well as chronic toxic effects.

 Toxic syndromes resulting from the intake of mycotoxins by man and animals are known as mycotoxicoses.

 Aflatoxins are the most important mycotoxins, which is produced by certain species of Aspergillus

 Aflatoxins are carcinogenic substances and may be present in a large number

of foods. This toxin can cause cancer, cirrhosis of the liver.

* **Methods of reduction of plant toxins:**

1. For some types of natural toxins, post- harvest processing treatments and

cooking of the plant result in destroying the endogenous toxic substances or

reduction of its toxicity.

2. Special care has to be exercised in selecting the food plants in limiting the

amount of intake.

* **Dietary supplemeand toxicity**

In the United States, manufacturers of dietary supplements are required to demonstrate safety of their products before approval is granted for commerce. Despite this caution, numerous adverse effects have been reported, including muscle cramps, hair loss, joint pain, liver disease, and allergic reactions, with 29% of the adverse effects resulting in hospitalization, and 20% in serious injuries or illnesses. The potential for adverse effects also occurs when individuals consume more than the necessary daily amount of vitamins or minerals that are needed to maintain normal body processes and functions. The incidence of adverse effects reported to the FDA were due to "combination products" that contain multiple ingredients, whereas dietary supplements containing a single vitamin, mineral, lipid product, and herbal product were less likely to cause adverse effects related to excess supplementation.

Among general reasons for the possible harmful effects of dietary supplements are: a) absorption in a short time, b) manufacturing quality and contamination, and c) enhancing both positive and negative effects at the same time. The incidence of liver injury from herbal and dietary supplements is about 16–20% of all supplement products causing injury, with the occurrence growing globally over the early 21st century.

* **Aristolochic Acid**

Aristolochic acids are nephrotoxic and carcinogenic phytochemicals found in many plant species, particularly the birthworts. Among the most well-known nephrotoxic syndromes, aristolochic acid nephropathy or “Chinese herbal nephropathy” is characterized by rapidly progressive and hypocellular interstitial nephritis and fibrosis with end-stage renal disease as well as uroepithelial malignancies.18 Nephrologists will be familiar with the large European case series following ingestion of

* **Amygdalin/Laetrile/Vitamin B17**

Amygdalin is a naturally occurring plant glycoside found in the seeds and pits of various fruits and nuts. A semisynthetic form of amygdalin called laetrile—also marketed as vitamin B17, although not a vitamin—is produced from hydrolysis of amygdalin obtained from apricot kernels. Upon ingestion, amygdalin and laetrile are both hydrolyzed by intestinal beta-glucosidase, releasing a cyanide anion. Hydrogen cyanide production after oral ingestion of amygdaline (laetrile) can cause fatal cyanide

* **Vitamin D Intoxication**

Vitamin D sterols are available in various forms and will be familiar as an essential component of management of hypocalcemia and hyperparathyroidism in chronic kidney disease-mineral bone disorder. The measurement of vitamin D levels and the recognition and supplementation of insufficiency or deficiency are now a widespread paradigm in primary care. An increase in reports of intoxication with vitamin D since 2010—a trend distinct among vitamins—indicates an evolving practice (both medical and

* **Heavy Metal Contamination of Plants and Medicines**

Soil contamination with heavy metals leading to bioaccumulation in herbal and medicinal plants and subsequent toxicity is of additional concern. The medical literature contains published analyses of levels of metals, as determined by spectrometry, in important plants particular to many regions of the world. Studies in plants have shown variable accumulation of a variety of metals and metalloids in plants with further differences among parts of the plant (roots, stems, or leaves) and the

**Genetic Susceptibility Influences Nephrotoxicity—Transport and Biotransformation**

Early assessments of nephrotoxic risk simply considered high renal blood flow and filtration and concentration of toxins into urine to be sufficient to cause injury. Understanding of this vulnerability to toxicity has broadened. The kidneys are involved in the elimination of xenobiotics, environmental agents, and metals through filtration, secretion, and metabolism. The mechanisms of tubular transport and biotransformation and their contribution to nephrotoxicity have been recently reviewed.28