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AN OVERVIEW: PHARMACOLOGY

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ABSTRACT

Plants are an important source of biologically active substance, therefore they have been used for medicinal purposes, since ancient times. Plant materials are used as home remedies, im over-the-counter drug products, dietary supplements and as raw material for obtention of phytochemicals. The use of medicinal plants is usually based on traditional knowledge, from which their therapeutic properties are oftenly ratified in pharmacological studies. Nowadays, a considerable amount of prescribed drug is still originated from botanical sources and they are associated with several pharmacological activities, such as morphine analgesic, scopolamine, atropine, galantamine, quinine, paclitaxel, vincristine and vinblastine, as well as digitalis glycosides. The versatility of biological actions can be attributed to the huge amount and wide variety of secondary metabolites in plant organisms, belonging to several chemical classes as alkaloids, coumarins, flavonoids, tannins, terpenoids, xanthones, etc. The large consumption of herbal drugs, in spite of the efficiency of synthetic drugs, is due to the belief that natural products are not toxic and have fewer side effects, the preference/need for alternative therapies, and their associated lower costs. In developing countries, herbal medicine is the main form of health care. In Brazil, where there is one of greatest biodiversity of plants in the world, pharmaceutical assistance programs, such as “Living Pharmacies”, have a prominent role in spreading the rational use of medicinal plants mainly for poor people, under recognition by World Health Organization (WHO).

INTRODUCTION:

Pharmacology is the branch of biology concerned with the study of drug action where a drug can be broadly defined as man-made, natural,or endogenous (from within the body) molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism(sometimes the word pharmacon is used as a term to encompass these endogenous and exogenous bioactive species). More specifically, it is the study of the interactive that occur between a living organism and chemicals that effect normal or abnormal biochemical function. If substances have medicinal properties, they are considered pharmaceuticals.

The field encompasses drug composition and properties, sybthesis and drug design, molecular and cellular mechanisms, organ/systems mechanisms, signal transduction/cellur communication, molecular diagnostics, interactions, toxicology, chemical biology, therapy, and medical applications and antipathogenic capabilities. The two main areas of pharmacology are pharmacodynamics and pharmacokinetics. Pharmacodynamics studies the effects of a drug on biological systems, and Pharmacokinetics studies the effects of biological systems on a drug. In broad terms, pharmacodynamics discusses the chemicals with biological systems. Pharmacology is not synonymous with pharmacy and he two terms are frequently confused. Pharmacology, a biomedical science, deals with the research, discovery, and characterization of chemicals which show biological effects and the elucidation of cellular and organismal function in relation to these chemicals. In contrast pharmacy, a health services profession, is concerned with application of the principles learned form pharmacology in its clinical settings; whether it be in a dispensing or clinical care role. In either field, the primary contrast between the two are their distinctions between direct-patient care, for pharmacy practice, and the science-oriented research field, driven by pharmacology.

The origins for clinical pharmacology date back to the Middle Ages in Avicenna's *The Canon of Meidicine*, Peter of Spain's Commentary on Isaac, and John of St Amand's *Commentary* on the *Antedotary of Nicholas.* Clinical pharmacology owes much of its foundation to the work of William Withering. Pharmacology as a scientific discipline did not further advance until the mid-19th century amid the great biomedical resurgence of that period. Before the second half of the nineteenth century, the remarkable potency and specificity of the actions of drugs such as morphine, aquinine and digitalis were explained vaguely and with reference to extraordinary chemical powers and affinities to certain orangs or tissues. The first pharmacology department was set up by Rudolf Buchheim in 1847, in recognition of the need to understand how therapeutic

drugs and poisons produced their effects. Early pharmacologists focused on natural substances, mainly plant extracts. Pharmacology developed in the 19th century as a biomedical science that applied the principles of scientific experimentation to therapeuric contexts. Today pharmacologists use genetics, molecular biology, biochemistry, and other advanced tools to transform information abour molecular mechanisms and targets into therapies derected against disease, defects or pathogens, and create methods for prefentative care, diagnostics, and ultimately personalized medicine.

TYPES OF PHARMACOLOGY:

The discipline of pharmacology can be; divided into many sub disciplines each with a specific focus.

Clinical Pharmacology:

Clinical pharmacology is the basic science of pharmacology with an added focus on the application of pharmacological principles and methods in the medical clinic and towards patient care and outcomes.

Neuropharmacology:

Neuropharmacology is the study of the effects of medication on central and peripheral nervous system functioning.

Psychopharmacology:

Psychopharmacology, also known as behavioural pharmacology, is the study of the effects of medication on the psyche(psychology), observing changed behaviours of the body and mind, and how molecular events are manifest in a measurable behavioural form. Psychopharmacology is an interdisciplinary field which studies behavioural effects of psychoactive drugs. It incorporates approaches and techniques from neuropharmacology, animal behaviour and behavioural neuroscience, and is interested in the behavioural and neurobiological mechanisms of action of psychoactive drugs. Another goal of behavioural pharmacology is to develop animal behavioural models to screen chemical compounds with therapeutic potentials. People in this field(called behavioural pharmacologists) typically use small animals (e.g. rodents) to study psychotherapeutic drugs such as antipsychotics, antidepressants and anxiolytics, and drugs of abuse such as nicotine, cocaine and methamphetamine. **Ethopharmacology** (not to be confused with ethnopharmacology) is a term which has been in use since the 1960s and derives from the Greek word *ethos* meaning character and “pharmacology” the study of drug actions and mechanism.

CARDIOVASCULAR PHARMACOLOGY:

Cardiovascular pharmacology is the study of the effects of drugs on the entire careiovascular system, including the heart and blood vessels.

PHARMACOGENETICS:

Pharmacogenetics is clinical testing of genetic cariation that gives rise to differing response to drugs.

PHARMACOGENOMICS:

Pharmacogenomics is the application of genomic technologies to drug discovery and further characterization of older drugs.

PHARMACOEPIDEMIOLOGY:

Pharmacoepidemiology is the study of the effects of drugs in large numbers of people.

SAFETY PHARMACOLOGY:

Safety pharmacology specialises in detecting and investigation potential undesirable pharmacodynamic effects of new chemical entities (NCEs) on physiological functions in relation to exposure in the therapeutic range and above.

SYSTEMS PHARMACOLOGY:

Systems pharmacology is the coding system principles in the dield of pharmacology.

TOXICOLOGY:

Toxicology is the study of the adverse effects, molecular targers, and characterization of drugs or any chemical substance in excess (including those beneficial in lower doses).

THEORETICAL PHARMACOLOGY:

Theoretical pharmacology is a relatively new and rapidly expanding field of research activity in which many of the techniques of computational chemistry, in particular computational quantum chemistry and the method of molecular mechanics, are proving to be of great value. Theoretical pharmacologists aim at rationalizing the relation between the activity of a particular drug, as observed experimentally, and its structural features as derived from computer experiments. They aim to find structure-activity relations. Furthermore, on the basis of the structure of a give organic molecule, the theoretical pharmacologist aims at predicting the biological activity of new drugs that are of the same general type as existing drugs. More ambitiously, it aims to predict entirely new classes of drugs, tailor-made for specific pruposes.

POSOLOGY: Posology is the study of how medicines are dosed. This depends upon various factors including age, climate, weight, sex, elimination rate of drug, genetic polumophism and time of administration. It is derived from the Greek words *posos* meaning and *logia* "study of".

ENVIRONMENTAL PHARMACOLOGY: Environmental pharmacology is a new discipline. Focus is being given to understand gene-environment interaction, drug-environment interaction and toxin-environment interaction. There is a close collaboration between environmental science and medicine in addressing these issues, as healthcare itself can be a cause of environmental damge or remediation. Human health an ecology are intimately related. Demand for more pharmaceutical products may place the public ar risk through the destruction of species. The entry of chemicals and drugs into the aquatic ecosystem is a more serious concern today. In addition, the production of some illegal drugs pollutes drinking water supply by releasing carcinogens. This field is intimately linked with Public Health fields.

EXPERIMENTAL PHARMACOLOGY:

Experimental pharmacology involves the study of pharmacology through bioassay, to test the efficacy and potency of a drug.

DENTAL PHARMACOLOGY:

Dental pharmacology relates to the study of drugs commonly used in the treatment of dental disease.

SCIENTIFIC BACKGROUND:

The study of chemicals requires intimate knowledge of the biological system affected. With the knowledge of cell biology and biochemistry increasing, the field of pharmacology has also changed subsrantially. It has become possible, through molecular analysis of receptors, to design chemicals that act on specific cellular signaling or metabolic pathways by affecting sites directly on cell-surface receptors (which modulate and mediate cellular signaling pathways by affecting sites directly on cell-surface teceptors(which modulate and mediate cellular signaling pathways controlling cellular function).

A chemical has, form the pharmacological point-of-view, various properties. Pharmacokinetics describes the effect of the body on the chemical (e.g. half-time and volume of distribution), and pharmacodynamics describes the chemicla's effects on the body (desired or toxic).

Medication is said to have a narrow or wide *therapeutic index* or *therapeutic window*. This describes the ratio of desired effect to toxic effect. A compound with a narrows therapeutic index (close to one) exerts its desired effect at a dose close to its toxic dose. A compound with a wide

therapeutic index(greater than five) exerts its desired effect at a dise substantially below its toxic dose. Those with a narrow margin are more difficult to dose and administer, and may require therapeutic drug monitoring (examples are warfarin, some antiepileptics, aminoglycoside antibiotics). Most anti-cancer drugs have a narrow therapeutic margin: toxic side –effects are almost always encountered ar doses used to kill tumors.

MEDICINE DEVELOPMENT AND SAFETY TESTING:

Development of medication is a vital concern to medicine, but also has strong economical and political implications. To protect the consumer and prevent abuse, many governments regulate the manufacture, sale, and administration of medication. In the United States, the main body that regulates pharmaceuticals is the Food and Drug Administration and they enforce standards set by the United States Pharmacopoeia. In the Eurpoean Union, the main body that regulates pharmaceuticals is the EMA and they enforce standards set by the European Pharmacopoeia.

The metabolic stability and the reactivity of a library of candidate drug compounds have to be assessed for drug metabolism and toxicological studies. Many methods have been proposed for quantitative predictions in drug metabolism. If the chemical structure of a medicinal compound is altered slightly, this could slightly or dramatically alter the medicinal properties of the compound depending on the level of alteration as it relates to the structural composition of the substrate or receptor site on which it exerts its medicinal effect, a concept referred to as the structural activity relationship (SAR). This means that when a useful activity has been identified, chemists will make many similar compounds called analogues, in an attempt to maximize the desired medicinal effect(s) of the compound. This development phase can take anywhere from a few years to a decade or more and is very expensive.

These new analogues need to be developed. It needs to be determined how safe the medicine is for human consumption, its stability in the human body and the base form for delivery to the desired organ system, like tablet or aerosol. After extensive testing, which can take up to 6 years, the new medicine is ready for marketing and selling.

As a result of the long time required to develop analogues and test a new meidicine and the fact that of every 5000 potential new medicines typically only one will ever reach the open market, this is an expensive way of doing things, often costing over 1 billion dollars. To recoup this outlay pharmaceutical companies may do a number of things.

- Carefully research the demand for their potential new product before spending an outlay of company funds.

- Obtain a patent on the new medicine preventing other companies form producing that medicine for a certain allocation of time.

DRUG LEGISLATION AND SAFETY:

In the United States, the Food and Drug Administation (FDA) is responsible for creating guidelines for the approval and use of drugs. The FDA requires that all approved drugs fulfil two requirements:

1. The drug must be found to be effective against the disease for which it is seeking approval (where 'effective' means only that the drug performed better than placebo or competitors in at least two trials).
2. The drug must meet safety criteria by being subject to animal and controlled human testing.

Gaining FDA approval usually takes several years. Testing done on animals must be extensive and must include several species to help in the evaluation of both the effectiveness and toxicity of the drug. The dosage of any drug approved for use is intended to fall within a range in which the drug produces a therapeutic effect or desired outcome. The safety and effectiveness of prescription drugs in the U.S. is regulated by the federal Prescription Drug Marketing Act of 1987.

The Medicines and Healthcare products Regulatory Agency (MHRA) has a similar role in the UK.

EDUCATION:

Students of pharmacology are trained as biomedical scientists, studying the effects of drugs on living organisms. This can lead to new drug discoveries, as well as a better understanding of the way in which the human body works.

Students of pharmacology must have detailed working knowledge of aspects in physiology, pathology and chemistry. During a typical degree they will cover areas such as (but not limited to) biochemistry, cell biology, basic physiology, genetics and the Central Dogma, medical microbiology, neuroscience, and depending on the department's interests, bio-organic chemistry, or chemical biology.

Modern Pharamacology is highly interdisciplinary. Graduate programs accept students from most biological and chemical backgrounds. With the increasing drive towards biophysical and computational research to describe systems, pharmacologists may even consider themselves mainly physical scientists. In many instances, Analytical Chemistry is closely related to the studies and needs of pharmacological research. Therefore, many institutions will onclude pharmacology under a Chemistry or Biochemistry Department, especially if a separate Pharmacology

Department. Does not exist. What makes an institutional department independent of another, or exist in the first place, is usually an artefact of historical times.

Whereas a pharmacy student will eventually work in a pharmacy dispensing medications, a pharmacologist will typically work within a laboratory setting. Careers for a pharmacologist include academic positions (medical and non-medical), governmental positions, private industrial positions, science writing, scientific patents law, consultation, biotech and pharmaceutical employment, the alcohol industry, food industry, forensics/law enforcement, public heath, and environmental/ecological sciences.

SCOPE OF PHARMACOLOGY:

HISTORY:

It is of intellectual interest to the physician to know how drugs are discovered and developed. Often in the past, this was based on folklore or intelligent observation (e.g. digitalis leaf, penicillin). Nowdays, new drugs are mostly developed by the organic chemist working with a pharmacologist, increasingly from basic knowledge about key molecular targets. Usually some sort of biological screen is used to select among organic molecules for optimum pharmacological activity.

FRANCOIS MAHENDIE (1783-1855): A French physiologist laid down the dictum "Facts and facts alone are the basis of science". Experimental procedures with animals are the testing grounds for determination of drug action.

CLAUDE BERNARD (1813-1878): Worked in Magendie's lab, investigated the plant extract curare and proposed a site of action for this agent.

RUDOLPH BUCHHEIM (1820-1879): In 1847 Buchheim established the first laboratory devoted to experimental pharmacology in the basement of his home in Dorpat which is known is known as the cradle of experimental pharmacology.

OSWALD SCHMIEDEBERG (1838-1921): In 1872 Schmiedeberg set up an institute of pharmacology in Strasbourg, France (Germany at that time) which became a mecca for students who were interest in pharmacological problems.

J.N. LANGLEY (1852-1925 AND SIR HENRY DALE 1875-1968): pioneered pharmacology in England, taking a physiological approach.

JOHN J. ABEL (1857-1938): established the first chair of pharmacology in the U.S.A. (U. Michigan, 1891) after training in Germany. Able went to Johns Hopkins in 1892, and trained many U.S. pharmacologists. He is known as "The Father of American Pharmacology".

The Second world war was the impetus for accelerated research in pharmacology (the war time antimalarial program) in the U.S., and introduced strong analytical and synthetic chemical approaches.

CHEMISTRY: Chemical structures of drugs can provide information about mechanism of action, pharmacokinetics, stability, and metabolic fate.

STRUCTURE-ACTIVITY RELATIONSHIP- A modification of the chemical structure of a drug may accentuate or dimish its pharmacological effects, often providing clues as to the mechanism of action. A picture of the biological reactive site (the receptor) can be developed in such studies. Also, drugs are metabozed by body systems, which may convert the parent drug to a more active or a less active form. The drug structure can be modified to enhance or diminish the rate of metabolic conversion.

SITES OF ACTION- The organ or cellular target of drug action.

DRUG RECEPTORS- Macromolecules in cells or cell membranes with which drugs interact to exert their effects. Usually the interacting forces are reversible ionic and Van der Waals bonds of relatively low energy, but sometimes covalent bonds are formed (e.g. organophosphate insecticides).

PHARMACODYNAMICS: The effect of the drug on the body. Pharmaco-dynamics is the study of the relationship of drug concentration and the biologic effect (physiological or biochemical). For most drugs it is necessary to know the site of tissue. For example, the drug effect may be localized to the brain, the meuromuscular junction, the heart, the kidney, etc. Often the mechanism of action can be described in biochemical or molecular terms. Most drugs exert effects on several organs or tissues, and have unwanted as well as therapeutic effects. There is a dose-response relationship for wanted and unwanted (toxic) effects. Patiend factors affect drug responses-age, weight, sex, diet, race, genetic factors, disease states, trauma, concurrent drugs, etc.

PHARMACOKINETICS – The effect of the body on the drug. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Thus, it is important to know the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.

ABSORPTION (ORAL OR PARENTERAL)- A drug must be absorbed and achieve adequate concentration at its site of action inorder to produce its biological effects. Thus, when a drug is applied to a body surface (e.g., g.i. tract, skin, etc.), its rate of absorption will determine the time for its maximal concentration in plasma and at the receptor to produce its peak effect.

DISTRIBUTION- The blood, total body water, extracellular, lymphatic and cerebrospinal fluids are involved in drug movement throughout the body. Depending upon its chemical and physical properties, the drug may be bound to plasma proteins or dissolved in body fat, delaying its progress to its sites of action or excretory mechanism.

METABOLISM- This is how certain drugs are handled by the body in preparation for their elimination and includes the fate of drugs-biotransformation (e.g., hydrolysis, conjugation, oxidation-reduction).

EXCRETION- The kidney is the most important organ for drug excretion but the liver, lung and skin are also involved in drug elimination. Drugs excreted in feces are mostly derived form unabsorbed, orally ingested drugs or from metabolites excreted in the bile and not reabsorbed by the intestine. The physical and chemical properties, especially the degree of ionization of the drug, are important in the rate of excretion.

BIOLOGICAL FACTORS MODIFYING PHARMACOLINETIC ASPECTS- Normal variations occur in population pharmacokinetic constants (absorption rates, elimination rates). Other factors include age, weight, obesity, edema, concurrent diseases, other drugs (various interactions including effects on protein binding or metabolic rate), diet, dose interval and route of administration, genetic variations in elimination rate.

CLINICAL PHARMACOLOGY AND THERAPEUTICS:

INDICATIONS AND THERAPEUTIC USES- Emphasis is placed on the therapeutic use of drugs for the treatment of disease in clinical pharmacology, internal medicine and therapeutics. There are specific clinic disorders or disease entities foe which a given drug may be presceibed and the physician must weight the potential benefit of drug use against the risks of adverse effects.

CONTRAINDICATIONS AND FACTORS (E.G., LIVER DISEASE) MAY MODIFY DRUG ACTION- Where detoxification of the drug by the liver is important, it is important to know that the presence of disease or organ pathology may influence the actions of a drug. Conditions such as age, pregnancy, concomitant administration of other drugs and disease may alter the patient's response to a given drug.

POSOLOGY- is an archaic term describing dosage regimens. Consideration of dosage schedules is a part of pharmacokinetics.

BIOAVAILABILITY- The fraction of drug administered which is actually absorbed and reaches the systemic circulation following oral dosing. Preparations of the same drug by different manufacturers may have a different bioavailability.

PRESCRIPTION WRITING- It is important that the physician write clear, error-free directions for the drug provider (pharmacist) and for the patient. Physicians must guard against prescribing too many drugs, or preparations of little value. Drugs of unproven clinical value should be avoided, as well as potentially toxic agents if drugs equally effective but less dangerous are available. Risk-benefit and cost-benefit should be considered. Drugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way. A particular manufacturer may be specified if the physician has reason to believe a better or more reliable preparation is available from that manufacturer.

DRUG NOMENCLATURE- In addition to its formal chemical name, a new drug is usually assigned a code name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the marker, a United States Adopted Name (USAN) is selected by the USAN Council which is sponsored by:

1. The American Medical Association
2. The American Pharmaceutical Association
3. The United Stats Phamacopeial Convention

TOXICOLOGY:

That aspect of pharmacology that deals with the adverse effects of chemical agents. Toxicology is concerned not only with drugs used in therapy but also with the other chemicals that may be responsible for household, environmental or industrial intoxication.

FORENSIC TOXICOLOGY- Addresses medicolegal aspects of the use of chemicals that are harmful to animals or man. Analytical chemistry and fundamental toxicological principles are hybridized to underlie this aspect of toxicology. Nonetheless accidental poisoning with drugs is a health problem of major significance. More than ¼ of the fatalities and about ½ of all poisonings occur in children under 5 years of age. All common household articles that are poisonous should be made unavailable to children, and poisonous rodenticides and insecticides should not be placed in the home.

CLINICAL TOXICOLOGY- Focuses on toxic events that are caused by or are uniquely associated with drugs or other chemicals.

PHARACOVIGILANCE- The area of pharmacology that focuses on the effects of drugs on patient safety. It involves the characterization, detection, and understanding of adverse events associated with drug administration, including adverse drug reactions, toxicities, and side effects that arise as a consequence of the short- or long-term use of drugs. Adverse drug. Adverse drug reactions, including drug-drug interactions, are estimated to be a major cause of mortality of

inpatients and also lead to significant increases in duration of hospiralization. No drug is free of toxic effects. Some untoward effects of drugs are trivial, but others are serious and may be fatal. Side effects often are predictable from a knowledge of the pharmacology of a particular drug. Examples of chemicals or drug-induced toxicities are given below:

ALLERFIC REACTIONS- The number of serious allergic reactions to drugs involving antigen-antibody reactions is low but when they occur the pgysician must have sufficient knowledge to manage these problems.

BLOOD DYSCRASIAS- Thses are very serious and sometimes fatal complications of drug therapy. They include: agranulocytpsis, aplastic anemia, hemolytc anemia, thromhocytopenia and defects on clotting factors.

HEPATOTOXICITY AND NEPHROTOXICITY- Beacuse many chemicals and drugs are eliminated and metabolized by the liver and kidney, damage to these organs is seen commonly.

TERATOGENIC EFFECTS- The thalidomide tragedy dramatically emphasized that drugs may adversely influence fetal development.

BEHAVIORAL TOXICITY- This is a term sed to describe suppression of normal anxiety, reduction in motivation, impairment of memory and learning, distortion of judgement, impairment of reflexes, adverse effects on mood, etc.

DRUG DEPENDENCE AND DRUG ABUSE- The repeated administration of some chemicals may lead to drug dependence. Drugs likely to be abused and upon which drug dependence may develop are the various psychopharmacological agents such as opiates, barbiturates, amphetamines, nicotine and ethanol. Dependence on tobacco (nicotine) is also well known.

CARCINOGENESIS: Carcinogenesis is a delayed type of toxicity with a latency of many years.

PHARMACOGENETIC TOXICITIES: Certain generically- predisposed individuals have a markedly toxic reaction to certain otherwise safe drugs. Examples are prolonged apnea after succinylcholine, or malignant hyperthermia associated with anesthetics.

PHYTOPHARMACEUTICALS OF PLANTS:

Herbal drugs are consumed by three-quarters of the world's population in the treatment of mainly chronic diseases, particularly headache, rheumatological disorders and asthma. In the developing countries, the population relies basically on medicinal plants ofr primary health acre, since modern medicine is expensive and not easily accessible. However, the consumption of herbal drugs is also large in developed countries. Phytotherapy is popular in many countries of Western Europe. Since people believe that either herbal drugs are devoid of side-effects or seek a healthier life style.

Americans usually buy herbal products as a dietry supplement in the United States, aiming at preventing aging and diseases like cancer, as well as diabetes.

Herbal drugs have some features which distinguish themselves considerably from synthetaic drugs. Herbal medicines are always formed from a cimplex mixture of chemical acompounds (*eg. Scutellaria baicalensis* has over 2000 components), and they may be constituted be many plants, therefore herbal drugs show an ample therapeutic usage. It is quite common to find a medicinal plant with several therapeutic properties. The combination of either maby plants, containing diverse bioactive stronder effect, therefore, permitting a reduction of dosage, which implies in lower risks of intoxication and undesirable side effects. As some diseases (e.g. AIDS or various types of cancer) possess a multi-causal etiology and a complex pathophysiology, a medical treatment may be more effective through well-chosen drug combination than a single drug. Ginkgolides A and B, isolated from *Ginkgo biloba* duly demonstrated a greater effect on the thrombocyte aggregation inhibition, when used as a mixture as opposed to what would be expected from the sum of the two compounds separately.

On the other hand, plant-based products do not possess a well-defined chemical composition, due partially to chemical complexity stated above. Hence, the active principles of herbal drugs are frequently unknown, in addition to their standardiation and quality control, being hardly achieved owing to mainly chemical variability in raw material. Secondary metabolites are the bioactive components from herbal drugs and their contents are strongly influenced by several factors: generic (genotypes, chemotupes), physiologic (circadian thythm, phenology, age), environmental (climate, sunlight exposure, water availability, soil, agro nomic conditions) and manufacturing conditions (harvesting storage and processing)

TABLE-1. MEDICINAL PLANTS USED TO PHARMACOLOGICAL ACTIVITY

S.NO	PHARMACOLOGY ACTIVITY	MEDICINAL PLANTS
1	Cough and cold	*Acorus calamus, polygonatum odoratum, Iris latea, humulus scandens, asarum sieboldii, pseudostellaria heterophylla, lepidium apetalum, lespedeza bicolor, hippophae rhamnoides, daucus carota, cari, carvi, pyrola rotundifolia, metaplexis japonica makino, origanum vulgare, veronicastrum sibiricum, lonicera japonica, valeriana officinalis, xanthium sibiricum, bidens parviflora, cephalanoplos segetum, anaphalis sinica, arctium lappa.*
2	Kidney and urethra problems	*Houttuynia cordata, Humulus scandens, Polygonum aviculare, Portulaca oleracea, Ranunculus sceleratus, Thlaspi arvense, Astragalus chrysopterus, Lespedeza biocolor, Daucus carota, Carum carvi, Diosuyros lotus, Cynanchum wilfordii, Metaplexis japonica, Leonurus pseudomacranthus, Origanum vulgare, Plantago depressa, Plantago asiatica, Valeriana officinalis, Cephalanoplos segetum*
3	Gastrointestinal disorders	*Rumex acetosa Linn, Portulaca oleracea, Sophora flavescens Ait, Lespedeza cuneate, Geranium sibiricum Linn, Daphne giraldii Nitsche, Hippophae rhamnoides, Daucus carota, Carum carvi, Origanum vulgare, Solanum nigurm Linn, Plantago depressa, Lonicera Japonica, Valeriana officinalis, Artemisia annua Linn, Bidens parviflora, Anaphalis sinica*
4	Cuts and wounds	*Gymnadenia conopsea, Polygonum viviparum, Paeonia obovata, Lepidium apetalum, Sedum aizoon Linn, Sanguisorba officinalis, Astragalus chrysopterus, Lespedeza cuneata, Oxalis acetosella Linn, Geranium sibiricum, Pyrola rotundifolia, Verbena officinalis Linn.*
5	Dermatological infections	*Rumex acetosa, Ranunculus japonicas Thunb, Sophora flavescens, Astragalus chrysopterus, Oxalis acetosella, Diospyros lotus, Verbena officinalis, Solanum nigrum, Artemisia annua, Bidens parviflora*
6	Fever and headache	*Hummulys scandens, Polygonum viviparum, Portulaca oleracea, Lespedeza bicolor, Origanum vulgare, Solanum nigum, Veronicastrum sibiricum, Artemisia annua, Anaphalis sinica*
7	Weakness and dizziness	*Polygonatum odoratum, Gymnadenia conopsea, Pseudostellaria heterophylla, Lepidium apetalum, Lespedeza bicolor, Carum carvi, Cynanchum wilfordii, Metaplexis japonica*
8	Menstrual disorders	*Ranunculus sceleratus, Paeonia obovata, Actinidia arguta, Pyrola rotundifolia, Verbena officinalis, Leonurus pseudo-macranthus, Origanum vulgare*
9	Ophthalmological problems	*Lespedeza cuneata, Tribulus terrestris Linn, Diospyros lotus, Solanum nigrum, Plantago depressa, Plantago asiatica*
10	Liver complaint	*Iris lacteal, Gymnadenia conopsea, Trobulus terrestris, Actinidia arguta, Plantago depressa, Plantago asiatica.*
11	Respiratory problems	*Houttuynia cordata, Ranunculus sceleratus, Lespedeza cuneata, Diospyros lotus, Solanum nigrum*
12	Heart diseases	*Polygonatum odoratum, Valeriana officinalis*
13	Toothache	*Acorus calamus, Asarum sieboldii*

TABLE-2. PHARMACOLOGICAL PROPERTIES OF MEDICINAL PLANTS

S.NO	MEDICINAL PLANTS	PHARMACOLOGICAL USES
1	*Portulaca oleracea*	Alkaloid extract may possess anti-inflammatory properties
2	*Iris lacteal*	Containing more than seven kinds of flavonoids but seldom pharmacological research
3	*Gymnadenia conopsea*	Antiallergic effect
4	*Hourruynia cordata*	Anti-inflammatory and virucidal effects
5	*Humulus scandens*	Antibacerial, antihypertensive, and anti-phlogistic properties
6	*Polygonum viviparum*	Antioxidative activity
7	*Rumex acetosa*	Antimuragenicity and antigenotoxic activity, but seldom pharmacological research
8	*Plantago depressa*	Hypoglycemia and lipids regulating effects
9	*Plyfonum aviculare*	Diuretic, antihypertensive, antibacterial, and antioxidant effect
10	*Carum carvi*	Antioxidant, hepatoprotective,and diuretic properties
11	*Pseudostellaria heterophylla*	Antifungal and immunostimulating activites
12	*Xanthium sibiricum*	Bacteriostatic and antifungal activities
13	*Tribulus terrestris*	Having several effects on central neural system, sex function, and muscular system
14	*Ranunculus japonicas*	Analgesic and anti-inflammatory effects
15	*Paeonia obovate*	Hypoglycaemic activity and immunocompetence of paeoniflorin
16	*Thlaspi arvense*	Antibacterial and antifungal activities

17	*Sedum aizoon*	Improving the immune function and relieving swelling and pain
18	*Plantago asiatica*	Antiviral and immunomodulatory effects
19	*Sanguisorba officinalis*	Antimicrobial activity
20	*Lonicera japonica*	Anit-inflammatoty activity
21	*Valeriana officinalis*	Having effect on circulatory system and respiratory system
22	*Polygonatum odoratum*	Hypoglycaemic effects
23	*Acorus calmus*	Reduction of body temperature and potentiation of hypnotic activity
24	*Lespedeza cuneata*	Contains tannins
25	*Oxalis acetosella*	Seldom report on physiological activity
26	*Geranium sibiricum*	Antibacterial and anti-inflammatory activities
27	*Sophora flavescens*	Contains matrine
28	*Actinidia argute*	Contains sesquiterpenes, monoterpenes, bebzene, and other compounds
29	*Daphne giraldii*	Anti-inflammatory analgesic activity
30	*Astragalus chrysopterus*	Contains soyasaponin, triterpenoid, glycoside daucosterol, beta-sitosterol, and other compounds
31	*Lespedeza bicolor*	Contains ethyl caffeare, caffeic acid, protocatechuic acid, betulinic acid, β-sotosterol and many active compounds
32	*Asarum sieboldii*	Antinociceptive effects
33	*Hippophae rhamnoides*	Antiodidant and immunomodulatory properties

34	*Solanum nigrum*	Gastric antiulcerogenic effects
35	*Pyrola rotundifolia*	Anti-inflammatory and analgesic activites
36	*Origanum vulgare*	Antimicrobial and cytotoxic activites
37	*Lepidium apetalum*	Contains flavonoids
38	*Cynanchum wilfordii*	Contains more than eight c21 steroidal glycosides
39	*Metaplexis japonica*	anticancer activity and improving immune function
40	*Verbena officinalis*	Anti-inflammatory and analgesic activity
41	*Leonurus pseudomacranthus*	Seldom report on physiological activity
42	*Veronicastrum sibiricum*	Anit-inflammatory and analgesic activities
43	*Daucus carota*	Hepatoprotective activity
44	*Diospyros lotus*	Antioxidant and antiproliferative activity
45	*Anaphalis sinica*	More than twenty components were isolated and many flavonoids were identified
46	*Ranunculus sceleratus*	Many chemical compounds were detected, but seldom pharmacological research
47	*Bidens parviflora*	Antihyperlipidemia, anti-inflammatory activities and protecting stomach
48	*Cephalanoplos segetum*	Contains high content of chlorogenic acid, but seldom pharmacological research
49	*Artemisia annua*	Antibacterial and antioxidant activites
50	*Arctium lappa*	Anit-inflammatory activity

PHYTOMEDICINE DRUG DEVELOPMENT PROCESS:

The current phytodrug development process has introduced gaps and lapses that are unfavourable to botanical –drug interaction studies as an integrated step. The argument often is concerning the usefulness of such studies especially where these products have been used therapeutically for centuries without such information. The world Health Organization promotes drug development from traditional medicines partly due to the saving in time and cost that makes the products affordable and accessible, leading to cheaper and cost-effective primary healthcare it offers its teeming population of users. The fast tracking is besed on the assumption that the substantial experience from the long history of human use increases the chances that a remedy will be effective and safe, and that precautions will be known. Conventional drug development is slow and expensive and often the finished products are unavailable and unaffordable to resource-limited countries, unless when made available by donors from high-income countries, under heavily subsidized schemes. For most phytomedicines, drug development from complimentary and alternative medicines usually follows a "reverse pharmacology" approach.

The first step is to select a remedy for development, through a retrospective treatment-outcome study or an ethnobotanical survey to identify medicinal plants used in the treatment of target disease conditions. This step usually will yield insufficient clinical information but is often a good guide to identification of plants and remedies for a given ailment. This is because the traditional medicine practitioners often do not have enough records as regards observed patient status as well as progress and treatment outcome and their perception of the efficacy and limitations of their remedies is subjective. Generally also their ability to accurately diagnose a disease condition may be inadequate because a lot of similar symptoms which may present in entirely different disease conditions may be treated with the same remedy. Thus often time, same remedies are employed in the treatment of 'fevers', 'stomach paina', et cetera. Therefore a lot of the information collected ar this stage is largely vague, needing evidence-driven scientific evaluation.

The second step usually spins off the first. Following the analyses of the collated remedies, treatment claims and subsequent plants identification, two essential elements are added to the ethno botanical survey by performing an organized treatment of a fairly large sample size, aimed at generating clinical information and evidence of efficacy in the presentation and progress of an episode of the target disease and statistically correlating treatment with reported clinical recovery as the marker of effectiveness.

Step three involves further research on a selected candidate remedy, to determine the possible pharmacological basis for the therapeutic claim through bioassays. Also at this pre-clinical stage, standardization and characterization of raw materials, intermediates and extracts are commenced, to generate quality control specifications data and chemical finger printing and identification of markers that can be used for monitoring of batch-to- batch uniformity.

The last step is clinical studies, usually involving a dose optimization observsionsl study that will help select the safest and most efficacious dose through a dose-response phenomenon and finally a randomized controlled trial to compare the phytomedicine ot he gold standard treatment for the target for the target disease is conducted.

This 'short-cut' approach facilitates the production of standardized phytomedicines faster and more cheaply than conventional drugs. In recent times, advances in this drug development strategy employs great efforts in standardization of mono- and multi-component phyto-preparations using all available high-tech methods, screening of extracts and their constituents by intefration of modern molecular biological bioassays and controlled clinical studies, aimed ar evidence based phytotherapy. However, it is still deficient in pertinent steps that involve systematic studies in the systemic effect of the phytomedicines inclusive of pharmacokinetic, bioavailability and drug interaction investigations.

For any medicine, efficacy and safety are the major issues thus before proceeding to clinical studies, it is important to establish that the remedy is safe. Safety ofmedicines in comprehensive sense would consist of not just the absence of toxicity but also the ability to use it effectively in a manner that avoids adverse reactions, therapeutic failure, minimizing risk-benefit ratio associated with its use while promoting rational drug use. WHO guidelines state that: "If the product has been traditionally used without demonstrated harm, no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment". The guideline relies heavily on evidence of traditional use or recent clinical experience as sufficient proof for safety and also arguing that often times, the same plants are traditionally used both as a food and as a medicine and no toxicological tests are required for foods. Which are usually consumed in greater quantities than medicines. This may not be sufficient reason to de-emphasis detailed safety srudies for herbal medicinal products because, one may argue that most often herbs are used as spices and condiments in foods ar smaller quantities as foods than as medicines. The differences in dosing can introduce variation in an observed response. For example, *Zingiber officinale* has been used and tested as an antinauseant and antispasmodic agent with very goos results. Ginger has

been shown to be a potent inhibitor of thromboxane synthetase and thus prolongs bleeding tiem and persons taking warfarin or other drugs that affect platelet activity have beeb advised to refrain from taking ginger in tablet form. Using ginger as a soice dose not give same effect. Therefore, even when preliminary field studies show that a herbal medicinal preparation is of common and ancient use, with no known important to identify the interaction potential of such herb(s) using proper in vitro and in vivo models in the early stages of drug development. The essence is to obtain enough information that may be useful for providing warning and proper advice to patients in clinical practice and improve the safe utilization of the herb.

In the past, the focus to address the above issues has been on scientific standardization and appropriate regulatory controls in the manufacture of phytomedicines in the following areas:

1. Application of all available modern, high-tech methods to standardize phytopreparations before conducting systematic pharmacological investigations and clinical studies.
2. Using new molecular biological assays for screening of extracts and plant constituents to evaluate their exact pharmacological profiles, to elucidate the pharmacological basis of the claimed actions of the constituents of an extract and bioassay guided fractions thereby gain a better understanding of the various mechanisms underlying these pharmacological effects.
3. Controlled clinical studies paralleled by pharmacolinetic and bioavailability studies. However in addition, we propose one more research foucs in the area of;
4. Incorporation of conventional principles in studies addressing additional safety concerns such as herb-drug interaction for the clinical use of herbal medicines, early in the drug development process

KNOWLEDGE OF PHARMCOKINETICS OF MEDICINES:

There is limited information on the pharmacokinetics of herbal medicines even though their use either alone or in addition to conventional drugs is increasing. One of the major reasons is that for most of these multicomponent mixtures, their active ingredient(s) are not known. In addition, there is the difficulty of measuring the quantities of the actives in systemic circulation due to very low concentratons, arising from the very small amount per dose in the final product. These challenges have lead to the situation that most herb –drug interaction studies and case reports inliterature only evaluate the outcome of adding a herbal medicinal product to an existing conventional drug therapy and monitoring changes in pharmacokinetics and /or clinical response of the orthodox drug. The reverse is rarely the case. Therefore, a better understanding of the pharmacokinetics of herbal medicines is needed to support the predictability of botanical-drug interactions. Giant

strides in the availability of specific high-tech analytical methods and equipment has resuled to the fact complex extracts and phytoprepraration can be analyzed today, to quantify the major active, compounds, which are supposed to be tesponsible for the efficacy of an edtract. The effectiveness of these modern tools and processes has been illustrated in several reports. Also, they meet the quality standards of drug authorities with high reproducibility of pharmacological studies subjected to good clinical practice (GCP) and conform to clinical trials requirements.

MECHANISMS OF HERBAL-DRUG INTERACTIONS:

Oagulany still involved in interactions between phytomedicines and drugs, resulting in pharmacokinetic and pharmacodynamic interactions. Herbal medicinal products or botanicals share the same metabolic and transport proteins, including cytochrome P450 enzumes (CYP), glucuronosyltransferases (UGTs), and P- glycoprotein (Pgp), with over-the-counter and prescription medicines increasing the likelihood of drug-botanical interactions. In other words, herbal products can interact with drugs by affecting the biological processes that regulate their metabolism and elimination.

The family of enzymes known as the cutochrome P540s (CYPs) are involved in 75% of drug metabolism. These monooxygenase enzymes are located mainly in intestinal and liver cells and catalyzes several phase I metabolic processes of many prescription drugs. Of its many subtupes, CYP3A4 is one of the most important, being responsible for about 50% of CYP450 –mediated metabolism. Thus natual products interfering with actions and/or quantities of CYP3A4 have the potential to affect a high percentage of drugs to variable extents. One way that a natural product can alter the action of an enzyme is to modulate by up or down regulating it. Also precipitators may affect bioavailability by modulating absorption or first pass metabolism, altered protein binding, or pharmacological effect. Interactions between herbals and medications can be caused by either pharmacodynamic or pharmacokinetic mechanisms.

Pharmacodynamic interactions can occur when a herbal product produces additive, synergistic, or antagonist activity in relation to the conventional drug with no change in the plasma conventration of either herbal product or drug. Such interactions are related to the pharmacological activity of the interacting agents and can affect organ systems, receptor sites, or enzymes. A pharmacodynamic interaction may occur when herbals that possess antipoatelet activity are administered with antiplatelet/anticoagulant drugs, thus increasing the risk for bleeding. When Kava, a herbal that depresses the central nervous system (CNS) was administered concomitantly with CNS depressant drug alprazolam, a semicomatose state was induced. When a sedative

botanical like valerian is co-administered with diazepam or other such sleep inducing agents, a potentiation of sleeping effect could occur. In addition, herbals with the potential to cause organ toxicity may cause further risk of to toxicity when drugs with similar toxicity are administered concurrently, such as when the hepatotoxic herbal comfrey is given with large and prolonged doses of acetaminophen. An example of an antagonistic interaction is when an herbal with high caffeine content, such as guarana, is administered with a sedative-hypnotic.

In pharmacokinetic interactions on the other hand, the herbal changes the absorption, distribution, metabolism, protein binding, or excretion of a drug which results in altered levels of the drugs or its metabolites. The resultant alterations caused by the combination of drugs may or may not alter the dose-response relationship despite the change in the plasma levels and/ or drug disposition profile of the drugs because an observable pharmacodynamic chage will depend on the degree of change in systemic concentration.

ABSORPTION:

Absorption of drugs can be impaired when herbs that contain hydrocolloidal fibers, gums, and mucilage are taken together. Examples of scuh herbs include psyllium, thubarb, flaxseed, marshmallow and aloe gel. These herbals can bind to drugs preventing their absorption and, subsequently, reduce systemic availability of the compounds. Psyllium a herb with high content of mucilage, used in the treatment of constipation, inhibits the absorption of lithium. Herbal laxatives such as aloe latex, buckthorn, cascara sagrada, rhubarb and sienna can cause loss of fluids and potassium and can potentially increase the risk of toxicity with digoxin as well as reduction in the action of drugs that have a narrow therapeutic index (eg, digoxin, warfarin) due to the diarrhea.

DISTRIBUTION:

Salicylates can displace highly protein-bound drugs such as warfarin and carbamazepine form plasma proteins thereby increasing the adverse/toxic effects of the drugs. Meadowsweet and black willow herbs contain salicylates and can potentially interact with such drugs. Potential pharmacokinetic interactions can occur with displacement of a drug from protein binding sites. Drug displacement of highly protein-bound drugs by another compound may result in increased activity of the displaced drug. Althuogh displacement of protein-bound drugs has beeb described as a mechanism for potential drug interactions, there are no documented reports of herbal-drug interactions attributable to displacement of drugs from protein-binding siteds.

METABOLISM:

Licorice when used as an herb, not a sweetener decreases the metabolism of corticosteroids and the anticoagulant action of warfarin is enhanced by ginkgo and possibly by many other herbs. Change in renal clearance of a drug is another potential mechanism for producing herbal-drug interactions. Herbals that can inhibit tubular uptake or in other ways that can interfere with the renal clearance of a drug should be considered as having potential to produce pharmacokinetic herbal drug interactions.

Two important processes involved in drug disposition in man have been implicated in most of the current evidence of herbal-drug interactions. Several of the documented herb-drug interactions are pharmacolimetic innature, ivolving metabolizing enzymes related to oxidative metabolism by the cytochrome P-450 system (CYP) and / or the efflux drug transporter Pglycoprotein, with gewer evidence of the involvement of other enzymes such as glutathione S-transferases and urin=dine diphosphoglycronyltransfereases (UGTs) and more than half of all medications undergo metabolism by CYP3A4 substrates. Besides CYP3A4 which has beeb shown to be involved in significant pharmacokinetic reactions in humans, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E. Necause some herbals and varius drugs may be stbstrates of the same CYP isoenyme, either of them may inhibit or induce the activity of the enzyme –substrate affinity and concentration among other factors.

The other important system that significantly contributes to drug disposition in human is the P-glycoprotein drug transporter. It is a glycoprotein encodec by the MDRI gene and functions as a transmemnrane efflux transporter that pumps drugs out of cells as they try to ger into the intestinal wall from the gut lumen where they again become available for oxidative elimination from the body. They are found mainly in organs responsible for drug absorption or elimination, such as the intestine, liver, and kidneys and also present in many tissues. This drug efflux therefore limits the rate and extent of drug absorporters and drug-metabolizing enzymes a=can lead to lower therapeutic efficacy or greater toxicity. The P-glycoprotein has high transport capacity and broad substrate specificity thus it can transport a wide number of clinically relevant drug with structurally different features and belonging to different cclasses such as several anticancer drug, some HIV protease inhibit;ors, H_2 receptor antagonists, antiarrhythmics-(cardiac glycosides and calcium channe, blockes), immunosuppressive immunosuppresive agents, corticosteroids, antiemetic and antidiarrheal agents, analgesics, antibiotics, anthelmintics, antiepileptics, sedatives, antidepressants.

Drug that are substrates of CYP3A4 often affect P-glycoproteins as well, thus the interplay of both intestinal P-gp and CYP3A4 has a strong effect on the bioavailability of most orally administered drugs including

proton pump inhibitors (PPIs), cyclosporine, medazolam, talinolol, statins, HIV protease inhibitors and verapamil. Therefore concomitant intake of herbal medicinal products that are Pgp and /or CYP3A4 substrates with orthodox drugs has a higher potential for interaction. Studies have shoen that in cancer therapy several anticancer drugs(such as vincristine, vinblastine, vinotelbine, irinotecan, etoposide, decetaxel, and paclitaxel), as well as certain supportive care agents concomitantly and commonly used by cancer patients, such as ondansetron, fentanyl,morpine, loperamide, and domperidone can modulate P-glycoprotein and /or CYP isoenzymes. Thus, the modulation of intestinal and hepatic Pgp and CYP enzymes by herbal medicines represents a potentially ikportant mechanism by which the bioavailability of co-administered drugs can be modulated.

Inhibition or induction of metabolizing enzymes or drug transporters involved in the systemic disposition for drugs is the mechanism of most pharmacolinetic interactions elicited by herbs or their active constituents. Inhibition occurs when herb is able to decrease the normal activity level of a metabolic enzyme or drug transporter via a competitive or noncompetitive mechanism. Induction on the other hand is a much slower process involving gene regulation and expression of the corresponding gene or drug transporter. Discontinuation of the precipitaror usually brings enxyme levels bank to normal,making the process reversible. Induction of the ezymes involved in the metabolism and transport of chemotherapeutic when each is concurrently administered with St John's Wort. On the other hand, inhibition of CYP3A4 by grapefruit juice was responsible for the increase in plasma levels of felodipine when a 5mg table was taken with the juice. Some botanicals that actively inhibit CYP enzymes include evening primrose oil, kava, garli, *Ginkgo biloba*, *Echinacea purpurea*, milk thistle, while Pgp activity was shown to be inhibited by curcumin, piperine, green tea, quercetin, and silymarin. Ginseng and ginsenosides inhibit both CYP enzyme and Pgp.

In a broad sense, the mechanisms behind induction of metabolizing enzymes will include processes that involve enhanced translational efficiency, increased gene transcription rates, improved enzyme stability and ligand binding/other enzyme-related actions. However, the most commonly encountered is that involving the activation of certain unclear receptors in man. This mechanism has beeb further elucidated, giving rise tonew possibilities for the idenrification of herbal preparations capable of causing indctuion because the mechanistic knowledge about induction processes can be ab aid in the prediction of clinically relevant interactions.

Pregnane X receptor (PXR), the constitutive androstane receptor (CAR), and the vitamin D-binding receptor (VDR) are unclear receptors that have beeb idenitiied to be involved in the induction of metabolizing enzymes and some drug transporters. After activation by endogenous or exogenous ligands, these receptors form heterodimers with the 9-*cis* retinoic acid receptor (RXR) and bind to xenobiotic response elements in the target genes. Because of this, the transcription of the target genes is increased, leading to detoxification and elimination of xenobotics.

PXR, is one of the main transcriptional regulators of CYP3A4 and Pgp, whole possessing some transcriptional control over CYP2B6, CYP2C9, sulfotransferase (SULT), UGT1A1, flutatione S-transferases (GST), and MRP-2. Studies have shown that the activation of PXR is one of the main mechanisms behind induction fo metabolizing enzymes and frug transporters by herbal medicine.s the inductive capacity of SJW is mediated via this mechanim. Hyoerforin, a bioactive constituent in St John's wort, forms a complex with the ligand-binding domain of human PXR thereby activation the PXR and consewuently inducing CYP3A4 and CYP2C9 expression. Studies using gene reporter assays or measuring mRNA levels of CYP3A4 om human hepatocytes have also shown that gugulipid, or its chemical constituents guggulsterones, derived from the Mulul myrrh tree, hops, two traditional Chinese medicines (TCMs), Wu Wei Zi (*Schisandra chenensis Baill*) and Gan Cao *(Glycyrrhiza uralensis Fisch),* and theri selective constituents, carotenoids, especially β-carotene, and retinol have the potential to induce CYP3A4 by activationof PXR.

Both P-gp and CYP3A4 are abundantly expressed in the villus tip of enterocytes and hepatocytes, correspondibgly, both intestine and liver express significant conventrations of PXR. This is important because the transcriptional regulation of drut metabilizing enzymes is cell-mediated and tissue-selective, thus significant induction will not be found in tissues that have low concentrations of the receptors and exzymes when in contact with the relevant ligands. Known ligands of human PXR include rifampicin, dexamethasone, clortrimazole, and paclitaxel and all are established inducers CYP3A4.

Metabolizing enzymes are also induced to a lesser extent by other unclear receptors such as CAR and VDR. CYP2B gene is the main target of CAR but the expression of other hepatic genes, such as UGT1A1 and CYP2C9 and MDR-1 is also modulated by this receptor. VDR is the receptor responsible for modulating cytogenesis and and cell death in response to 1α, 25-dihydroxy vitamin D_3 as the ligand. In addition, it also regulates CYP3A$, CYP3B6 and CYP2C9. Though PXR has been shown to mainly regulate CYP3A4 edpression while CAR regulates CYP2B expression of several enxymes, meaning that the specificity is nor absolute but rather there is some overlap in

both the nuclear transcription fuction as well as the ligandibinding capacity and the extent of induction will vary depending on the ligand, tissue involved. Conseqyebtly, more than one exzyme modulated by dufferent receptors may be responsible for an observed effect in a herb induced interacrion. For example, PXR, CAR and the arly hydrocarbon receptor (AhR) are all known to modulate the overall UGT1A1 response to flavonoids, though the AhR is mainly responsible for the UGT1A11 response to flavonoids, though the AhR is mainly responsible for the UGT1A1 expression.

In vitro screening for potential inhibition or induction of CYP enzymes by various herbals is gaingin momentum, but data about the inductive capacity of herbal medicinal products and their interaction with nuclear receptors is scarce and mainly focused on PXR. However, with the discovery of the mechanistic processes involving nuclear receptors in the induction of metabolizing enzymes and drug transporters drug transporters, recent efforts to address these challenges are more optimistic.

CONCLUSION:

The term 'Herbal produts' has become a collowuial term which commonly regers to all types of preparations obtained from herbs, spices, roots, stems, leaves and other non-botanical materials of natural origin. They can be used therapeutically as prescription or over-the-counter medicines or even as cosmetics orally or topically. Plants are importat=nt sources of medicines and plant derived drugs came into use in modern medicine through the uses of plant materials as indigenous cure in folkore or traditional systems of medicine. The use of plant extracts and herbs as medicine preparations has been since the beginning of recorded time, probably origination form ancient China and Egypt. Over 80,000 species of plants are in use throughout the world. In the last century, roughly 121 pharmaceutical products were formulated based on the knowledge of plant use in traditional medicine from various sources and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant-drived ingredient.

Herbal medicine, phytotherapy, phytomedicine, nutracuticals, natural product medicine, complimentary & alternative medicine, ethnomedicien, botanicals, herbal medicinal product, dietary supplements and pgttopharmaceuticals are all terms used interchangeably to denote the use of botanicals in healthcare and are therefore used as such in this text. Increasing number of patients and consumers are using plant-based therapeutic products as complementary therapy in the treatment and management of chronic ailments such as tuberculosis, diabetes, hypertension, HIV/AIDS, cancer and diseases of endemicity and high recrudescence especially malaria, as well

as other social conditions like obesity, cigarette smoking and drug abuse. This upsurge in the use of phytomedicines is a global phenomenon, with more than 80% of people in Africa and Asia using herbal medicines and an increasing number in the Western world. It is estimated that 60% to 70% of the American population is taking botanical products.

In recent times many factors have contributed to the current surge in phyto medicne use. The therapeutic superiority of many plant extract over singly isolated constituents, as well as the bioequivalence of many phyto pharmaceuticals with synthetic chemotherapeutics is well documented. The gradual transition from the long-standing use of monodrug therapy in classical medicine to the new concept of a multidrug and multistage therapy is greatly promoting phytoherapeutics. There is a gradual shift from the orthodox use of mono-substance therapy and an increasing transition to multidrug therapy of patients with drug combinations, such as is done presently for the treatment of diabetes, acquired immune deficiency syndrome(AIDS) malaria, tuberculosis or hypertension.

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