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Research Article

PAST AND FUTURE OF PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF HERBAL DRUGS

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ABSTRACT

Aim: Plants are the most vital sources of medicines. Many people preferred plant based medicine for the improvement of their health conditions alone or in combination with others. In recent years, more and more Pharmacokinetic (PK) & Pharmacodynamic (PD) Parameters are applicable for investigation of active components in herbal medicine.
Background: The PK parameters includes Bioavailability (Cmax, tmax, AUC), Absorption rate constant(Ka), Volume of distribution, Distribution equilibrium, Distribution rate constant, Clearance, Half–life, 1st order ,0 order & mixed order kinetics, Elimination rate constant(Kel, Ka, Km) And PD parameters includes Drug- receptor binding, Drug-drug interaction. Few research studies reported that PK & PD parameters used for herbal drugs; such as Garlic, Ginger, Curcumin, Licorice, Vinca, Emblica officinalis, Schisandra chinensis, Rhizoma coptidis, Pueraria lobata, Herba Ephedrae, Nao-De-Sheng, Corydalis bungeana, Radix Aconiti Lateralis, Praeparata Rhubarb peony, Suan-Zao-Ren, Ginseng, Ginko, Green tea, Danshen, Ding quai, Kava, St John's wort, Grapefruit juice, Nauclea latifolia, Echinacea purpurea and Tobacco. PK & PD study of herbal drug is mainly used for drug development, identifying drugs biological properties, determination of drug concentration in body, drug efficacy.
C**onclusion:** This review discuss about the past and future PK and PD studies, benefits and future studies of herbal drugs and will be helpful for young researchers who are involved in the field of herbal plants and also provide commercialization of herbal products.

Keywords: Pharmacokinetic, Pharmacodynamic, Herbal drugs, Bioavailability, Clearance, Drug –drug interaction.

INTRODUCTION

Plants are one of the most important sources of medicines .It has been proved to be efficient enough to treat many diseases. In ancient years, about 60,000 years plants are used for therapeutic significance which was discovered in prehistoric graves [1]. Ayurveda, Sidha and Unani have a very rich history of Indian traditional medicine for their effectiveness. Ayurveda is the prehistoric science of life having a show up Sanskrit word Ayur means "Life" and "Veda" means "Knowledge". Ayurveda is defined as "The knowledge of living" or "The since of longevity". In these system there are many people preferred Ayurvedic medicines or products to improve their health conditions or as medicinal substance either alone or in combination with others. All the formulations specify in the Ayurvedic Formulary of India are still used in India, and recently, those composition have begun to extend worldwide [2, 3]. The World Health Organization approximated 80% of people worldwide rely on herbal medicines for component of their most important health care needs [4]. Herbal drugs are used by different advancements in different parts of the world for centuries to attack a large number of diseases. Herbal medicinal is now being used but their scientific evidence is not reported. The multiple reason for patient turning towards herbal therapies are as conventional system is costly or time consuming as compare with herbal medicine. A recent observational study indicates that the patients use herbal medicine & conventional medicine simultaneously which leads to adverse drug interaction and can leads to dangerous & raised serious concern among the medical science. Therefore this increases the necessity of PK and PD study for herbal plants [5]. Some herbal drugs of the recent studies on PK and PD parameters are listed in Table 1.

Table 1: Recent Studies on Pk & Pd Parameters of Plant

S.NO	HERBAL DRUG	PHARMACOKINETIC	PHARMACODYNAMIC	REFERENCE
1	*Garlic*	$T_{1/2}$ T_{max}, C_{max}, AUC, Cl, Ke, Vd	Systolic blood pressure (SBP), heart rate, cholesterol, dehydrogenises, superoxide dismutase, Over – anticoagulation	[1,6,7,8]
2	*Ginger*	C_{max}, T_{max}, $T_{1/2}$, AUC,	Over – anticoagulation	[1,9,10,11]
3	*Curcumin*	$T_{1/2}$, AUC CL , MRT , Vd, C_{max} , t_{max},	Not done	[12]

4	*Licorice*	t_{max}, C_{max}, $T_{1/2,}$ $_{AUC}$	Not done	[13]
5	*Vinca*	AUC, Vd, CL	Not done	[14,15]
6	*Emblica officinal's*	C_{max}, t_{max} , $T_{1/2}$, AUC	Not done	[16]
7	*Schisandra chinensis*	AUC, C_{max}, $T_{1/2}$, MRT, CL	Not done	[17,18]
8	*Rhizoma coptidis*	$T_{1/2}$, C_{max}, T_{max}, AUC	Not done	[17]
9	*Pueraria lobata*	T_{max}, AUC, $T_{1/2}$,	Not done	[19]
10	*Angelica pubescens Maxim*	C_{max}, Vd, $T_{1/2}$	Not done	[20]
11	*Herba Ephedrae*	T_{max}, C_{max}, AUC, $T_{1/2}$	Not done	[21]
12	*Corydalis bungeana Herba*	T_{max}, $T_{1/2}$, MRT, AUC	Not done	[22]
13	*Nao-De-Sheng (NDS)*	T_{max}, C_{max}, AUC	Not done	[23]
14	*Rhubarb peony*	T_{max}, C_{max}, $T_{1/2}$	Not done	[21]
15	*Suan-Zao-Ren (SZR)*	T_{max}, C_{max}, AUC, $T_{1/2}$	Not done	[24]
16	*Ginko*	Not applicable done	Spontaneous hyphema, Over - anticoagulation	[25]
17	*Green tea*	Not applicable done	Decreased anticoagulant effect	[26]
18	*Curbicin*	Not applicable done	Over – anticoagulation	[27]
19	*Danshen*	Tmax, C_{max}, AUC, $T_{1/2}$, MRT, CL	Over – anticoagulation	[1,26,28]
20	*Ding quai*	Not applicable done	Over – anticoagulation	[1]
21	*Kava*	Not applicable done	Semicomatose state, Reduced efficacy of levodopa	[29]
22	*St john's wort*	CL, Ke, Vd, $T_{1/2}$, AUC, C_{max}, T_{max}	Not done	[1, 30]
23	*Grapefruit juice*	CL	Not done	[32]
24	*Echinacea purpurea*	AUC, C_{max}, $T_{1/2,}$ CL	Not done	[33]
25	*Tobacco*	AUC, C_{max}, T_{max}	Not done	[33]

Pk And Pd Parameter

PK is defined as what the body does to the drug. It deals with the absorption, distribution, and elimination of drugs [34]. Absorption and distribution means of access drug molecules from the administration site to the blood and passage of drug molecules from blood to tissues correspondingly. Drug elimination occurs through biotransformation and by the passage of molecules from the blood to the outside of the body throughout urines, bile or other routes. PK has been generally applied to investigate the main active ingredient of herbal drugs [35]. the following situation may should be appropriate for PK study; route of drug administration, dose regimen, tissues to sample, sample times, analytical method, the animal species or, in clinical settings [36]. PK is determine by data generate on various drug interactions to be assume the Plasma kinetics, drug concentration, volume of distribution, half-life, clearance, drug elimination, determination of therapeutic level6 [37].

PD is the study defined as the effects of a drug on the body [38]. It is use for the study of relationship between drug concentration at the site of action, biochemical or physiological changes (genetic mutation, response sensitivity and drug-drug interaction) and molecular effect of drug. The effect of drug is determined by receptors binding side, post receptor effect & chemical interaction [37, 39, 40].

PK & PD analysis seeks to review the actions of a drug in the body, to understand the sources of variability in these activities fig.1, and to use this knowledge to design rational, and ideally individualized, dose regimens [36].

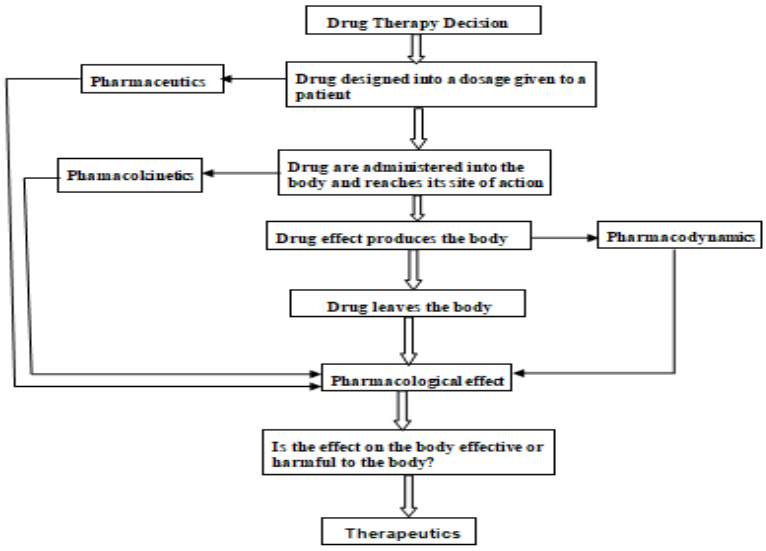

Fig.1: PK & PD study on the body.

Bioavailability

Bioavailability is explained as the rate and extent at which drugs become available in the systemic circulation. It is one of the most important characteristics of the drug development process, mainly for natural compounds or new molecular entity with important for biological activity [41]. The estimation of bioavailability is carry out by using the area under the curve (AUC), maximum plasma drug concentration (C_{amx}) and Time of peak plasma concentration (Tmax). More recently other parameters such as mean residence time (MRT) and half value duration (HVD) have been proposed to evaluate the rate and the profile of the concentration-time curves. Bioavailability Affected by: Dosage form, Dissolution and absorption of drug , Route of administration , Stability of the drug in the GI tract (if oral route), Extent of drug metabolism before reaching systemic circulation e.g. First Pass metabolism , Presence of food/drugs in GI Tract [42].

$T_{1/2} = 0.693 \times VD / CL$

VD = volume of distribution

CL = clearance

$$\text{Bioavailability} = \frac{\text{Quantity of drug reaching systemic circulation}}{\text{Quantity of drug administration}}$$

Time of peak plasma concentration

The maximum time for drug reaches to peak concentration in plasma is called as time of peak plasma concentration. The unit of t_{max} is hr. In the graph two peaks of identical height are observed, the first peak is measured as t_{max} and second peak is C_{max}. While each concentration is connected with a specific time in a pair wise manner (time, concentration) [34].

Area under curve

The plasma concentration between a drug and time after dose called “area under the curve” or AUC shown in fig.2. AUC gives the level of exposure of a drug and its clearance rate from the body [42]. By incorporate over time rather than looking at individual concentration measurements, a more accurate estimate of the overall exposure to the drug is obtained [43]. Such measurements have also been found to be important for assessing the net pharmacological response to a given dose of drug [44].

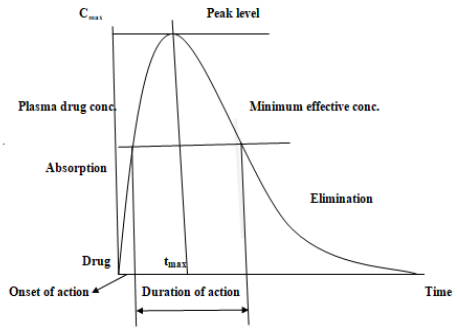

Fig. 2- Area under curve

Half-life

Time duration in which the amount of drug in the body is reduced by 50%. Therefore, in each following half-life few drugs are eliminated. After one half-life the amount of drug residual in the body is 50% after two half-life 25%, After 4 half-life the amount of drug (6.25%) is considered to be slight concerning its therapeutic effects in fig.3.The half-life of a drug depends on the clearance and volume of distribution. The elimination half-life is measured to be free amount of drug in the body [34].

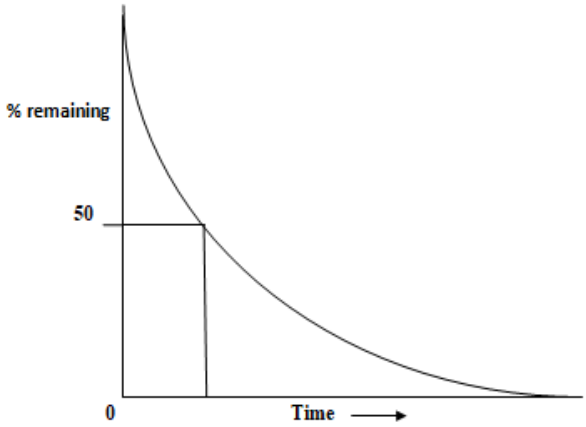

Fig. 3: Half -life curve showing % drug remaining with respect to time

Volume of distribution (VD)

The parameters are volume of distribution related to the amount of drug in the body and total plasma drug concentration. Drugs are distributed not every time between various body fluids and tissues according to their physical and chemical property. It can be measure the drug concentration in the blood.

VD will vary between different drugs according to:

- Water Solubility,
- Solubility of Lipid,
- Plasma or tissue protein binding properties

If a drug is thoroughly distributed to the tissues the first few doses disappear directly from the blood stream [42].

Plasma Protein Binding

Plasma protein binding is defined as the drugs can bind with several tissues present in the body. Two categories of plasma protein bindings are:

1. Blood

2. Extra vascular tissues.

Generally macromolecules such as proteins, DNA are interacting molecules. The proteins are mainly responsible for such interaction given in fig.4. The happening of complex structure with proteins is called as protein binding of drugs. A lot of drugs are bound to plasma proteins such as albumin, only free drug can bind at receptors site [43].

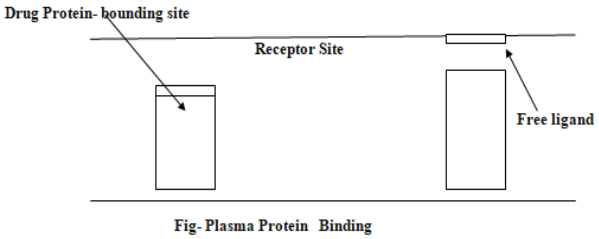

Fig.4:Plasma protein binding of drug at the receptor site

Mean Residence Time (MRT)

Mean residence time is the concentration of drug at a given time to residence time of individual molecules in the body. MRT is calculated by different amount of molecules present in the body at different time. Some drugs are having very short amount of time and other last longer. By using relative frequency of the residence time in the body, the graph can be plotted to obtained concentration-time curve in fig.5 [42].

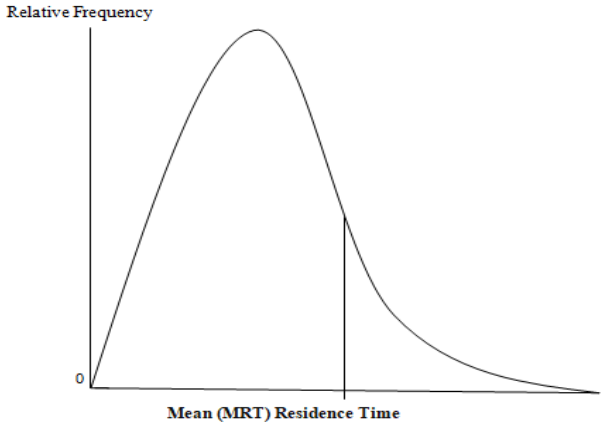

Fig.5:Mean Residence Time

Clearance

Clearance is determined by the ability of body to eliminate a drug. It is representing as a volume per unit of time. Further Clearance is defined as blood clearance (CL), plasma clearance (CLp), or clearance found the concentration of free drug (CL). Elimination of drug may arise as processes by liver, kidney and other organs [42, 44].

$$CL_{hepatic} + CL_{renal} + tCL_{other} = CL_{c\ system}$$

Drug-drug interaction

PD interactions can happen when herbal formulation gives additive, synergistic or antagonist activity in relation to conventional systems with no change in the plasma concentration. PD interactions are related to be pharmacological activity of interacting representative & can affect organs, receptor sites, or enzymes [40, 45].

Therapeutic drug monitoring (TDM)

TDM is define as the ability to utilize multiple statically statistics to assess an ever-changing clinical condition. TDM is commonly employed in the ICU. The principle of TDM in the ICU is to help highest clinical outcome, decrease toxicity, and make certain that the cost-effective drug treatment side effects. Research should be done on herbal drugs to known the pharmacokinetic and Pharmacodynamics is provided. TDM is significance in identification of Drugs that normally produce toxicity at different dosages to essential for therapeutic effects [46].

CONCLUSION

A lot of work is still essential to be done in this area due to requirement for the study of pharmacokinetic and Pharmacodynamics activity for various herbal medicines to estimate their safety, efficacy and other parameters of the herbal drugs whose pharmacokinetic and Pharmacodynamics parameter is not conventional. Pharmaceutical study must go further focusing on pharmacological helpfulness of herbal drugs but also increase their efficacy for humankind to fully rise from their inherent therapeutic potentials.

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