Mathematical model of drug delivery using Anti-cancerous Herbal drugs

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ABSTRACT

Pharmacokinetics deals with the distribution of drugs, chemicals, tracers or radioactive substance among the various compartments of the human body. Here, Mathematical modeling sheds light on kinetics part of the cancer treatment using Herbal drugs. There is extensive and consistent evidence that high fruit and vegetable intakes are associated with decreased risks of many cancers. Mounting evidence over the past decade suggests that carotenoides, Lycopene, processed tomato products, Turmeric etc, are associated with reduced risk of cancer and producing therapeutic benefits and lowering the risks on adverse effects. Drug Concentration taken as a parameter initially. The two compartment analysis has been done to observe the behavior of lycopene in the body. Future research on this topic would help to identify safe and effective anticancer herbal drugs and will further explore their mechanism of action using more effective modeling approach.

Keywords Pharmacokinetics, Drug delivery, carotenoids, Lycopene, Tomato, Turmeric

Introduction

Pharmacokinetics [1] is defined as the study of the time course of a drug and its metabolite levels in different fluids, tissues, and excreta of the body and of the mathematical relationship required to develop models to interpret such data. Pharmacokinetics seems very much useful in nutrition/herbs research. Whole world is practicing herbal medicine to avoid maximum side effects .In India; practice "Ayurveda ". The science of Ayurveda [2] is supposed to add a step on to curative aspects of cancers. There are many herbs like Aswagandha, Amla, Basil, Rakta vrntaka (Tomato), Neem, Turmeric etc. which has significant role in cancer care. The character, behavior and properties (mechanical characterization) of herbs or plants play crucial role in drug research. Nutritional scientists [3] have an important role to play in the development of chemopreventive agents. For example, many individual phytochemicals, including lycopene from tomatoes, are worthy of consideration as candidate chemopreventive agents and will need extensive preclinical development and translation into human Phase I, II, and III studies. Traditionally, investigators pursuing chemopreventive strategies have been trained in pharmacology, carcinogenesis, or related fields with little opportunity to interact with nutritional scientists who are focusing on cancer prevention. It is imperative that barriers to interaction be identified so that transdisciplinary projects can be rapidly moved from concept into human trails.

Tomatoes are Lycopene rich food. Lycopene one of a family of pigments called carotenoids which occur naturally in fruits and vegetables was identified to be responsible for the beneficial effects of tomatoes. Lycopene is an antioxidant that once absorbed by the body, helps to prevent and repair damaged cells. In laboratory experiments, lycopene has been found to possess the most protective effects against free radicals within the entire carotenoid family [4]. In the past several years, two lines of emerging evidence have supported a role for lycopene in the prevention of certain malignancies, especially prostate cancer [5]. Epidemiologic and animal studies [6] provide support for a relationship between high intakes of carotenoids from fruits and vegetables with reduced risk of several malignancies including prostate cancer. First, antioxidant properties of lycopene (Lycopersicon esculentum). have been established [7]. Given the relatively high concentrations of lycopene in the tissues of many individuals, and the potential role of oxidative stress in the formation or progression of cancers, a potential anticancer influence of lycopene has been hypothesized. Secondly, a number of epidemiologic studies have suggested that individuals with relatively high intake of lycopene, particularly from tomato products, have a lower risk of prostate cancer [8]. Serum and tissue lycopene levels have also been inversely related to the risk of lung and prostate cancers. Lycopene functions as a very potent antioxidant, and this is clearly a major important mechanism [9] of lycopene action.

Anticancerous Herbal Drugs

Herbal drugs are in practice because they are easily available, with tailored cost and with less side effects. This paper gives us available literature regarding researches on anticancerous herbs.List of Ayuervedic anticancerous herbs [2] are given for future research. Turmeric powder has been used for medicinal purpose in Asia .several animal and in vitro studies have been done to check the capability of turmeric and its active component curcumin to suppress the growth of a variety of tumor cells [10]In this way there are many herbs like Basil(Tulsi ,an Indian herbs) , Amla , Haldi(Indian Name) etc has anticancerous properties.Our aim in this paper to focus light on these hidden herbs which are beneficial in cancer research.

Biochemistry and Physiology (Lycopene)
Lycopene [11] is a natural pigment synthesized by plants and microorganisms but not by animals. It is a carotenoid, an acyclic isomer of b-carotene, and has no vitamin A activity. It is hypothesized that prostate cancer patients perhaps lack the ability to isomerize dietary lycopene and therefore do not absorb it efficiently.

Characteristics of Lycopene
It is an acyclic hydrocarbon [12] carotenoid (containing 11 conjugated double bonds in the all-trans form. It lacks provitamin A activity, but has an exceptionally high singlet oxygen quenching ability. Epidemiological studies of lycopene and cancer have correlated increased tomato intake with lower incidence of gastrointestinal, stomach, and prostate cancers while decreasing serum values of lycopene increases the risks for various types of cancer. Lycopene is an effective inhibitor of cell growth and DNA synthesis in human cancer cell cultures and suppresses mammary tumor development in SHN mice and DMBA rat tumor models.
Another autopsy study showed that beta-carotene and lycopene were the predominant carotenoids in the liver, kidney, and lung tissue. A third study found that lycopene was a predominant carotenoid in the human prostate and in a mouse model with implants of human prostate adenocarcinoma.

Mechanisms of Action of Lycopene
Lycopene cyclase[9] is an enzyme found in tomatoes that can convert lycopene to beta carotene by catalyzing the formation of two beta rings at each end of the linear carotene. The red color of tomatoes is due to the accumulation of lycopene resulting from a down-regulation of the lycopene cyclase gene (CrtL), which has been cloned from tomato (Lycopersicon esculentum).
Nonetheless, most research on the preventive effects of dietary intake of tomato products have focused on lycopene. Increased ingestion of tomatoes and tomato products containing lycopene has been shown to be associated with decreased risk of chronic diseases including cancer. For example, serum and tissue lycopene levels have been inversely related with prostate cancer risk.Each of these classes of plant-derived foods may have unique phytochemicals that interact with the host to confer a preventive benefit by regulating enzymes important in metabolizing xenobiotics and carcinogens, by modulating nuclear receptors and cellular signaling of proliferation and apoptosis, and by acting indirectly through antioxidant actions that reduce proliferation and protect DNA from damage. Although there is significant evidence supporting the actions of lycopene as a potent antioxidant, there are a number of other potential mechanisms through which tomato products providing lycopene and other phytochemicals may reduce the risk for chronic diseases, including common forms of cancer and heart disease.

Antioxidant Activity
Carotenoids such as lycopene convert singlet state oxygen to its ground triplet state by absorbing and then dispersing excess excited state energy in the form of heat. Singlet oxygen [12] can react with unsaturated compounds such as polyunsaturated fatty acids but may be intercepted by physical quenching. Lycopene has an exceptionally high singlet oxygen quenching ability, twice that of beta-carotene. Lycopene also interacts with other active oxygen species, such as hydrogen peroxide, which can generate the hydroxy radical known to induce strand scission in DNA and nitrogen dioxide, an air pollutant causing cell membrane damage. These changes may promote DNA mutations conducive to tumor generation and membrane alterations that allow for proliferation and metastases. Oxidative stress [9] is recognized as one of the major contributors of increased risk of cancer.

Antiproliferative behavior
Lycopene has been found to inhibit proliferation of several types of cancer cells, including those of breast, lung, and endometrium. Scientist investigated whether various carotenoids [13] present in foodstuffs were potentially involved in cancer-preventing present action on human prostate cancer. The effects of 15 kinds of carotenoids on the viability of three lines of human prostate cancer cells, PC-3, DU 145 and LNCaP, were evaluated. Acyclic carotenoids such as phytofluene, ζ-carotene and lycopene, all of which are present in tomato, also significantly reduced cell viability.

Physiological pharmacokinetic model
For nutrition research compartmental modeling is perfect. compartmental modeling involves [14] setting up a system of compartments and connecting those compartments with mathematical equations to describe the transfer of material from one compartment to another .Then simulation performed to test the model behavior against experimental data. Understanding dose response and nutrient disposition is a key use of modeling and a compartmental model of lycopene disposition was recently publishes by Diwadkar Navsariwala et. al..A physiological pharmacokinetic model was developed for lycopene based on current knowledge of the metabolism of carotenoids in humans [15,16] In 2003; A physiological pharmacokinetic model [17] was developed to describe the disposition of lycopene, delivered as a tomato beverage formulation in five graded doses (10, 30, 60, 90, or 120 mg), for a phase I study in healthy male subjects (five per dose).seven compartment model has been taken to show the disposition. WinSAAM and ANOVA software had been used for calculation.

Mathematical pharmacokinetic model
Absorption , Distribution ,Metabolism, Excretion are four important part of pharmacokinetics process.Due to highly non -linear nature of the pharmacokinetic parameter estimation, variation in parameter values from one subject to another, and sparse data available in clinical and laboratory settings a perfect and systematic approach is needed to model, estimate and analyze Lycopene pharmacokinetics. Such an approach must include: i) a method for compartmental model order selection, ii) a perfect and systematic method of estimating Lycopene

pharmacokinetic parameters, and Lycopene concentration in different Compartments, and iii) a method of validating the selected model and the estimation results.

Two compartment model

In pharmacokinetics[2] we assumed body as multi compartment structure. Pharmacokinetics equations describe the relationship between the dosage regimen and the profile of drug concentration in the blood over time. Pharmacodynamics equations describe the relationship between drug concentration-time profile and therapeutic and adverse effects. By controlling the plasma concentration time profile of a drug; we can ensure that the patient receives optimum treatment. Two compartment model has been taken to introduce herbal drugs disposition. Here first order equation has been taken for model.

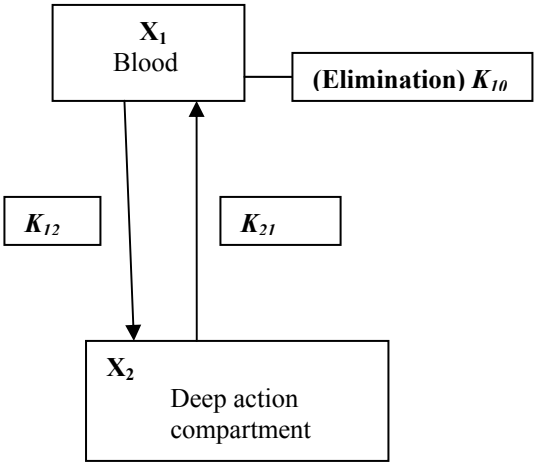

Figure 1**:** Two compartment model

Here, X_1 be initial amount taken in first compartment.

K_{12} and k_{21}: Rate constant for drug transfer between compartment 1 and 2, the blood and the deep action compartment. $\mathbf{K_{10}}$: rate constant for elimination of drug from blood (The Lycopene elimination from the body is through kidneys and the Liver.)

The differential equations for the above model are:

$$d X_1/dt = -(K_{12} + K_{10}) X_1 + K_{21} X_2 \quad \text{Eq.1}$$

$$d X_2/dt = K_{12} X_1 - K_{21} X_2 \quad \text{Eq.2}$$

The initial conditions are known: t = 0 , we suppose that at this time there is no drug in the second compartment .when we take any drug it first distribute in whole body from one compartment to another then elimination takes place . Here initial dose in first compartment is 30 mg.

$$X_1(0) = 30\text{mg}, X_2(0) = 0, \quad \text{Eq.3}$$

We had taken assumed some values in one compartment which is function of time. When absorption start concentration will be start decreasing exponentially (Fig. 2) Fig Using the method of an exponential pealing we now estimate β_{11}, λ_1, β_{12}, λ_2. Since the method of exponential pealing demands sufficiently large values of t .we neglect the points in which t is less then 1 hour.

We have $X_1(t) = \beta_{11} e^{\lambda_1 t} + \beta_{12} e^{\lambda_2 t}$

First we estimate β_{11} and λ_1 by fitting the straight line

$\text{Ln } X_1(t) \approx \text{Ln } \beta_{11} + \lambda_1 t$

To the given assumed data the values of β11 and λ_1 are found to be $\beta_{11} = 3.03$ and $\lambda_1 = -.26$

Since initially the amount in the first compartment was 30 mg .so we have , $\beta_{12} = 26.97$

In the second step we fit the straight line

$\text{Ln } [X_1(t) - \beta_{11} e^{\lambda_1 t}] \approx \text{Ln } \beta_{12} + \lambda_2 t$ to the given assumed data, The value of λ_2 is found out to be $\lambda_2 = -3.05$

Therefore we have, $X_1(t) = 3.03\, e^{-.26 t} + 26.97\, e^{-3.05 t}$

Using the above relation the value of $X_1(t)$ at different times are found .From calculation it is clear that the difference between the assumed and calculate value is inversely proportional to time.

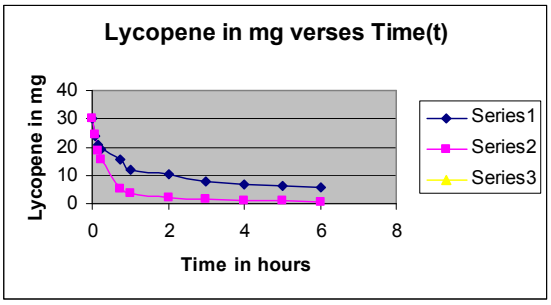

Figure 2. comparative study of assumed value[17] and calculated lycopene values

In Fig 2. Elimination of lycopene has been shown which is decreasing with respect to time. Drugs perform there role when they enter inside the body .when they enters inside body concentration increases then slowly slowly decreases exponentially.

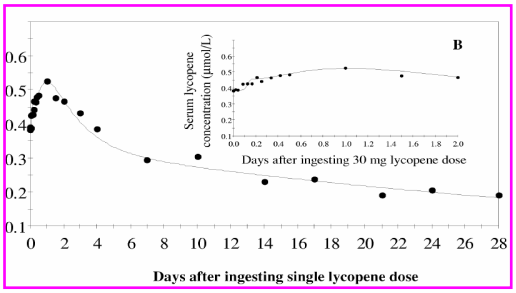

Figure .3 Pharmacokinetic model fit (line) for the serum lycopene concentrations (closed circles) in representative subjects at 5 dose levels.

The insets show the model fit for the first 2 days (48 hours) after dosing. After dosing, the first lycopene peak was observed at around 6 hours (0.25 days), followed by a temporary decline and a second peak at around 24 hours (1day)[17].

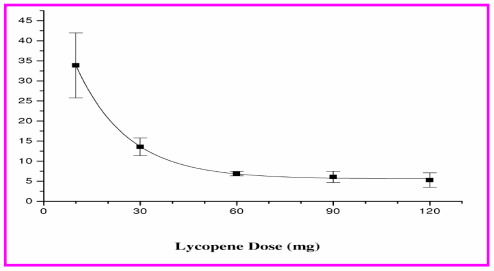

Figure 4. Exponential decreases in percent absorption with increasing dose (mg), suggesting a dose-dependent saturation in absorption. The data points were fit for y = 5.6 + 28.3 exp [(10-x)/15.9][17].

At this time the vast majority of research activity has focused on anticancerous allopathic drug, whereas little effort has targeted herbal/Ayuervedic anticancerous drugs .

Results and discussion

On the basis of Figure 2, 3 and 4 following observations has been made.

Drugs perform there role when they enter inside the body. When they enters inside body concentration increases due to anatomical and mechanical characterization of the soft biological tissues and after sometime decreases exponentially.In Figure 3 the insets show the model fit for the first 2 days (48 hours) after dosing. After dosing, the first lycopene peak was observed at around 6 hours (0.25 days), followed by a temporary decline and a second peak at around 24 hours. Figure 4 shows the same pattern as per our observation in figure2 and figure3.which correspond to the physiological compatibilities.

Conclusion

Role of mathematical modeling and simulation in nutrition research plays very important role in study of compartmental analysis of herbal drug kinetics. It may possible we can obtain useful parameters with the use of compartmental analysis if experimental data is known .If experimental data is known then method of exponential peeling has been used to determine the useful parameters such as absorption efficiencies, drug dosage, drug Concentration, drug dosage, drug scheduling, drug resistance, drug toxicity, and drug transfer coefficient, elimination rates and tissue metabolism of compounds. They play key role for supporting the nutrient transport. Use of mathematical modeling for anticancerous herbal drugs can not solve our problems totally but may be possible it will give new dimension to cancer research.

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