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Mathematical model in herbal drug (Kutki) kinetics

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Abstract
Picrorhiza kurroa (kutki) is an important medicine plant used in various herbal drug formulation possessing hepatoprotective activity. Various herbal drug P. kurroa as one of the constituents, were also analysed for picroside content. In the present study of Mathematical model in herbal drug (kutki) kinetics Medicinal plants have been traditionally used for treating several. Several leads from plant sources have been found as potential hepatoprotective agents with diverse chemical structures. Although, a big list of hepatoprotective phytomolecules was reported in the scientific literature, only a few were potent against various types of liver damages. Of which, picroside, kutkoside, hypophyllanthin, and glycyrrhizin have largely attracted the scientific community. In the present study we find that Calculated amount of kutki drug, picroside-1 and picroside-2 is maximum (32.58%), (49.5%) and (48.5%) in comparision to Experimental amount of drug in blood compartment.

Keywords: Kutki (Picrorhiza Kurroa), drug, picroside, hepatoprotective

1. Introduction
The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplification actions of body processes are necessary to predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principle to the various processes. To apply mathematical principles, a model of the body must be selected. A basic type of model used in pharmacokinetics is the compartmental model. Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one-compartment models. The compartments do not represents in the body. Compartmental models are termed deterministic because the observed drug concentrations determine the type of compartmental model required to describe the pharmacokinetics of the drug. This concept will become evident when we examine one and two compartment models.

To construct a compartmental model as a representation of the body, simplifications of body structure are made. Organs and tissues in which drug distribution is similar are grouped into one compartment. For example distribution into renal tissue for most drugs. Therefore, the highly perfused organs (e.g. heart, liver and blood disorder) often have similar drug distribution pattern, so these areas may be considered as one compartment. The compartment that includes blood (plasma), heart, lungs, liver, and kidneys is usually referred to a the central compartment or 1 and 2 the highly blood-perfused compartment. The other compartment that includes fat tissue, muscle tissue and cerebrospinal fluid is the peripheral compartment, which is less well perfume than the central compartment.

Another simplification of body processes concerns body over time. These changes with time are known as rates. The elimination rate describes the change in the amount of drug due to drug elimination over time. Most pharmacokinetics models assume that elimination does not change over time. The value of any model is determined by how well it predicts drug concentrations in fluids and tissues. Generally, it is best to use the simplest model that accurately predicts changes in drug concentration over time. If a one-compartment model is sufficient to predict plasma drug concentrations (and those concentration are of most interest to us), then a more complex (two-compartment or more) model is not needed. However, more complex models are often require to predict tissue drug concentrations. Drugs that do not extensively distribute into extravascular tissues, such as amino glycosides are generally well described by one compartment models. Extent of distribution is partly by the chemistry

of the agents. Amino glycosides are polar molecules, so their distribution is limited primarily to extracellular water. Drug extensively distributed in tissues (such as lipophilic drugs like the benzodiazepines) or that have extensive intracellular uptake may be better described by the more complex models.

1.1. Kutki

The Kutki is one of the major incomes generating non-timber forest products of India. It is known to be one of the oldest medicinal plants trade from the Himalayan zone. In Jumla, it is collected from government controlled alpine pastureland, national park and community managed land and sold to village trades who air lift the product to Nepalgunj to a wholesaler. The leaf, bark and underground part of the plants, mainly rhizomes are widely used in the Ayurvedic medicine systems. The owner occur in kutki during June-August and fruits occurs in kutki from end of September. The kutki turns in yellow colour at the starting of October. Kutki is easily distinguished by its elongate, stout creeping rootstock associated with withered leaf base. The skin of the rootstock is thick, wrinkled and prominently stratiated. The rhizome is evanescent inside hence can be easily compressed. Leaves are radical, spathulate and sharply serrated. Flower of this taxon is white or pale blue-purple in dense terminal spicate raceme. Fruits are borne in ovoid capsule. Kutki grows naturally in wild in alpine regions on rock scars as well as in organic soils. It is found in Himalayan region (Garhwal to Bhutan), Southeast Tibet, North Burma and West China. In India, Kutki distributed abundantly in Alpine Himalaya between 3500 to 4800m. It is found in rocky places of Himalaya. It refers to grow generally on the rock's crevices. It mostly grows on sloppy and mountains. After December, the plants remain under snow under the beginning of summer the snow melts and Kutki is regenerate from the dormant parts. The associated plants species of Kutki are: Bhedakhaja (Anemone tetrasepala), Bukephool (Anaphalisp), Bhojpatra (Betula utilis), Dhupi (Juniperus indica), Dhupguri, Jatamansi (Nardostachys grandiflora), Ratoghans (Geum elatum) and Sun pate (Rhododendron anthopogon). The harvesting season of Kutki is from October to December. However, the local people collect Kutki from May to December. The whole plant is pulled out manually Mostly men are involved in collection of this plant with long rhizome is easier to harvest. The taste of Kutki's root bitter in taste and has cooling effect. It is used as a cardiotonic, antipyretic, anthelmintic and laxative. It is also used in stomachic. It promotes an appetite and is useful in Kapha, biliousness, bellow fever, urinary discharge, hiccough, blood troubles, burning sensations, Leucoderma, and Jaundice, purifies the nurse's milk (Ayurveda).

Fig 1

Kutkin is the active principal of Picrorhiza kurroa and is comprised of kutkoside and the Iridoid glycosides Picroside-1 and 2. The herbal drug, in the form of dried roots and rhizomes, is prescribed in the treatment of several disease of the liver and spleen, and in cases of fever and asthma. There are different commercially available herbal formulations of kutki which contain Picroside-1 and Picroside-2 in different concentrations.

1.2. Uses of Kutki

The Root is bitter in taste and has a cooling effect. It is used as a cardiotonic, antipyretic, anthelmintic and laxative. It promotes an appetite and is useful in following diseases.

a. Diabetes
b. Blood disorder
c. Liver disorder
d. Cough
e. Asthma
f. Urinary problem
g. Digestive Problems

2. Components of Kutki

1. Kutki root powder comes from low growing plant that grows in higher elevations of Asia and has been used in Ayurvedic Medicine in India for hundreds of year and it has many benefits.
2. Kutki root is well known for supporting liver function and for normalizing liver enzymes and also helps to cool the body and at the same time boost the immune system.
3. Kutki root promotes the formation and power of bile from the liver. Kutki is well known for healing cirrhoses of the liver and most of the time powdered Kutki root is mixed with honey and taken three times a day and most of the time used in conjunction with liver cleansing herbs.
4. 3-4 gm of drug is generally given as antiperiodic and 0.6-1.2 gm as better tonic. Typical adult dosage is 400 to 1500 mg/day, with dosages up to 3.5 gm/day sometimes being recommended for fever and heart diseases.
5. Kutki roots also works well for ascites or fluid buildup in the abdomen caused by liver problems and Kutki helps with jaundice caused by liver problems. At the same time Kutki perk up a person appetite and can also work as a good herbal remedy for constipation.
6. Kutki Root is a powerful antioxidant thus helping to prevent disease of the cardiovascular system, strokes, and even cancer.
7. Kutki Root contains lots of powerful glucosides such as cucurbitacin, pictrohizin, benetic acid, vanillic acid, D-mannitol and kutkisterol many of which also help to lower cholesterol (In a study of over 100 subject with high cholesterol there was a significant drop in cholesterol by almost 30% with no side effects).
8. It is contains very powerful anti-inflammatory agents such as apocynin which is great for treating arthritis and also to prevent blockages of arteries by platelets and thus prevent heart attacks.

2.1 Purim (Component of Kutki)

The Natural therapy for healthy skin

2.1.1 Action: Combats skin disease: Purim's antiseptic, antibacterial, antifungal, anti-inflammatory, antiviral, wound healing and anti-allergic properties work synergistically to

treat skin infections. As a hepatostimulant, the drug improves liver function and its detoxifying property removes toxic metabolic products from the body. Purim provides symptomatic relief in skin allergies and dermatitis.

2.1.2 Eliminates worms: Purim's anthelmintic property is beneficial in controlling cutaneous (on the skin) manifestation of worm infections.

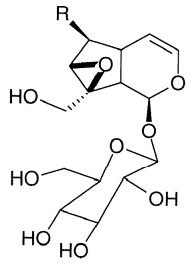
2.1.3 Indications

1. Acute and chronic dermatitis.
2. Hyperpigmentation in chronic dermatitis cutaneous manifestation of worm infections.
3. Acne vulgaris and acne rosacea associated with acneiform postulation.

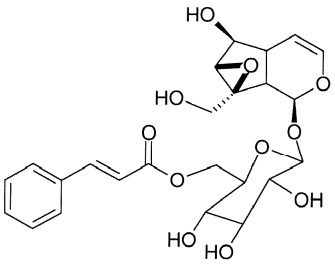
2.1.4 Key ingredients: Turmeric (Haridra) acts as an anti-inflammatory herb in both acute and chronic inflammation. It is extremely helpful in soothing skin allergies. Turmeric is a natural blood detoxifier and anti-microbial which helps alleviate skin diseases and enhances the complexion. The natural therapy for healthy skin

2.2. Picroside (component of kutki)

Picroside is an organic compound. The Chemical name of Picroside 1 and 2 is -dGlucopyranoside and β-D-glucopyranoside. The use of picroside Pre-treatment of PC12 cells the cell viability and decrease the level of intracellular reactive oxygen species (ROS) induced by glutamate. By DNA fragmentation and flow cytometry assay, picroside II (0.6 mg/ml) significantly prevented glutamate-induced cell apoptosis.



PK-II



PK-I

3. Mathematical Model

The one-compartment model is the frequently used mode in clinical practice. In structuring the model, a visual representation is helpful. The compartment is represented by an enclose square or rectangle, and rates of drug transfer are represented by straight arrows. The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving the compartment.

This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Some drug distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. Intravenous bolus dosing means administering a dose of drug over a very short time period. A common distribution pattern is for the drug to distribution pattern is for the drug to distribute rapidly in the bloodstream and to the highly perfused organs, such as the liver. Then, at a slower rate, the drug distribution may be represented by a two-compartment model. Drug moves back and forth between these compartments to maintain equilibrium. Digoxin, particularly when given intravenously, is an example of a drug that is well described by two-compartment pharmacokinetics. After an intravenous dose is administered, plasma concentration rise and then rapidly decline as drug distributes out of plasma and into muscle tissue. After equilibration between drug in tissue and plasma, plasma concentrations decline less rapidly. The plasma would be the central compartment, and muscle tissue would be the peripheral compartment.

Volume of Distribution

Until now, se have spoken of the amount of drug in a compartment. If we also consider the volume of the compartment, we can describe the concept of drug concentration. Drug concentration in the compartment is defined as the amount of drug is given volume, such as mg/L.

Concentration = amount of drug in body ÷ Volume in which drug is distributed = y/v

Volume of distribution is an important indicator of the extent of drug distribution into body fluids and tissues. V relates the amount of the drug in the body to the measured concentration in the plasma. Thus, V is the volume required to account for all of the drug in the body if the concentrations in all tissues are the same as the plasma concentration:

Volume of distribution=amount of drug÷ concentration

A large volume of distribution usually indicates that the drug distributes extensively into body tissues and fluids. Conversely, a small volume of distribution often indicates limited drug distribution.

Volume of distribution indicates the extent of distribution but not the tissues or fluids into which the drug distributes. Two drugs can have the same volume of distribution, but one may distribute primarily into muscle tissues. When V is many times volume of the body distribution, let us first imagine the body as a tank filled with fluid, as the body is primarily composed of water. To calculate the volume of the tank, we can place a known quantity of substance into it and then measure its concentration in the fluid.If the amount of substance and the volume of distribution can be calculated using the simplified equations:

$$y = V C$$

Where y = amount of drug in body.
V = volume of distribution.
C = concentration in the blood.

As with other pharmacokinetics parameter, Volume of distribution can vary considerably from one person to another because of difference in physiology or disease states. Something to note. The dose of a drug (y0) and the volume of a tank can be determined from the amount of substance added and the resulting concentration. Drug elimination complicates the determination of the volume of the body from drug concentrations. The amount of drug in the body are essentially the same thing because all of the dose goes

into the body. In this example, important assumptions have been made that instantaneous distribution occurs and that it occurs equally throughout the tank. In the closed tank, there is no elimination. This example is analogous to a one compartment model of the body after intravenous bolus administration. However, there is one complicating factor-during the entire time that the drug is in the body, elimination is taking place. So, if we consider the body as a tank with an open outlet value, the concentration used to calculate the volume of the tank would be constantly changing. We can use the relationship given in table for volume, amount of drug administered, and resulting concentration of distribution to estimate a drug's volume in a patient. If we give a known dose of a drug and determine the concentration of that drug achieved in the blood, we can calculate a volume of distribution. However, the concentration used for this estimation must take into account changes resulting from drug elimination, must take into account changes resulting from drug elimination, as discussed in other chapter. For example:
If 500 mg of Purim (component of drug) is administered intravenously and the blood concentration to be 5 mg/L just after the dose is given then

Volume of distribution = dose ÷ resuting concentration = y_0/c = 500/5 =100ml

The value of distribution is easily approximated for many drugs. for example, if the first 80 mg dose of gentamicin is administered intravenously and results in a peak plasma concentration of 8 mg/L, volume of distribution would be calculated as follows: The volume of distribution(V) = y_0/ c

3.1 Mathematical model for Action of Beta-Blocker

Beta-Blocker is the class of drug that use on the pressure and heart rate. Beta Blockers reduce the oxygen needs of this heart by reducing the heart rate. They are used as antihypertensive and antiarrhythmics to treat angina due to exertion and to case symptoms such as palpitations and tremors in patients who are troubled with anxiety states. They are used occasionally for migraine headaches (pain in the head). Beta-Blocker may be taken as tablet or given by injection possible side effects are nausea, insomnia, physical we ariness, diarrhea. Overdose can cause dizziness and fainting spells. Discontinuation of treatment with these drugs should be gradual (in sequence), not abrual (not in sequence) Beta-Blocker are not advised for people who suffer either with asthma or heart failure.
Beta-blocker is illustrated below:

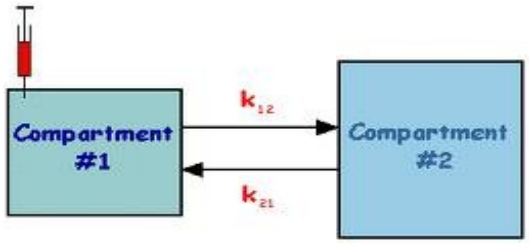


Fig 2

The Differential equation for above model is

$$\frac{dx_1}{dt} = -(a_{12} + a_{10})y_1 + a_{21}y_2 \quad (3.1.1)$$
$$\frac{dx_2}{dt} = a_{12}y_1 - a_{21}y_2 \quad (3.1.2)$$

The initial condition are known

$$y_1(0) = m, y_2(0) = 0 \quad (3.1.3)$$

In the equation (3.1.1) and (3.1.2) the (y_i) are the quantities of the drug at time in compartment i. The initial conditions meant that a quantity has been given at time t = 0. In compartment 1 we assume that at this time there is no drug in the second compartment. In practice only y_1 is measured for t = t_j where j= 1 to n. Clearly y_1 and y_2 are linear combination of $e^{\lambda_1}(t)$ and $e^{\lambda_2}(t)$ where y_1 and y_2 are the characteristic values of the differential system equation (3.1.1) and (3.1.2). We suppose that these characteristic values are real and negative. These properties comes from biochemical considerations.

$$y_1 = b_{11}e^{\lambda_1}(t) + b_{12}e^{\lambda_2}(t) \quad (3.1.4)$$
$$y_2 = b_{21}e^{\lambda_1}(t) + b_{22}e^{\lambda_2}(t) \quad (3.1.5)$$

Putting the values of y_1 and y_2 from (3.1.4) and (3.1.5) into (3.1.1) and (3.1.2) and identifying the coefficient of y_1 and y_2 then we get the algebraic relation:

$$b_{11}\lambda_1 = -(a_{12} + a_{10})b_{11} + a_{12}b_{21} \quad (3.1.6)$$
$$b_{12}\lambda_2 = -(a_{12} + a_{10})b_{12} + a_{12}b_{22} \quad (3.1.7)$$
$$b_{11}\lambda_1 = a_{12}b_{11} - a_{21}b_{21} \quad (3.1.8)$$
$$b_{12}\lambda_2 = a_{12}b_{12} - a_{21}b_{22} \quad (3.1.9)$$

Using the initial condition from equation (3.1.3) gives two relations:

$$b11 + b12 = m \quad (3.1.10)$$
$$b_{21} + b_{22} = 0 \quad (3.1.11)$$

In one experiment, the amount of drug in the blood compartment at different times are found to be shown in table 1.

Table 1

Time (in hrs)	Experimental datay1 (in gms)
0	3.5
0.08	2.82
0.17	2.43
0.25	2.25
0.75	1.88
1	1.77
2	1.40
3	1.11

Using the method of exponential pealing we now estimate b_{11}, λ_1, b_{12}, λ_1, Since the method of exponential pealing demands sufficiently large values of t we neglect the points for which t is less than one hour. We have

$$y_1(t) = b_{11}e^{\lambda 1}t + b_{12}e^{\lambda 2}(t) \quad (3.1.12)$$

First we estimate b_{11} and λ_1 by fetting the straight line

$$\ln y_1(t) \approx \ln b_{11} + \lambda_1(t) \quad (3.1.13)$$

To the given experimental data, the values of b_{11} and λ_1 are found to be λ_1= -0.256 and b_{11} = 2.85 since initially the amount in the first compartment was 3.5 gms. We have using equation (3.1.10), b_{12}= 0.68

In the second step we fit the straight line

$$\ln[y1(t) - 2.85e0{:}256\ ] \approx 1.078 + \lambda 2(t) \qquad (3.1.14)$$

To the given experimental data. The value of λ_2 is found out to be λ_2 = -0.82 therefore, from equation (5), we have

$$y_1(t) = 2.85e^{-0.256}(t) + 0.68e^{-0.82}(t) \qquad (3.1.15)$$

Using the above relation the value of y_1 at different times are found.

Table 2

Time (hrs)	Experimental data (gms)	Calculated data (gms)
0.00	3.5	3.52
0.08	2.82	3.34
0.17	2.43	3.22
0.25	2.25	3.11
0.75	1.88	2.51
1.00	1.77	2.08
2.00	1.4	1.56
3.00	1.11	1.19
4.00	0.9	0.93
5.00	0.69	0.70
6.00	0.48	0.4

3.1.1 Graph of Variation of the Beta blocker

It is clear that difference between the experiment and the calculate is inversely proportional to time.

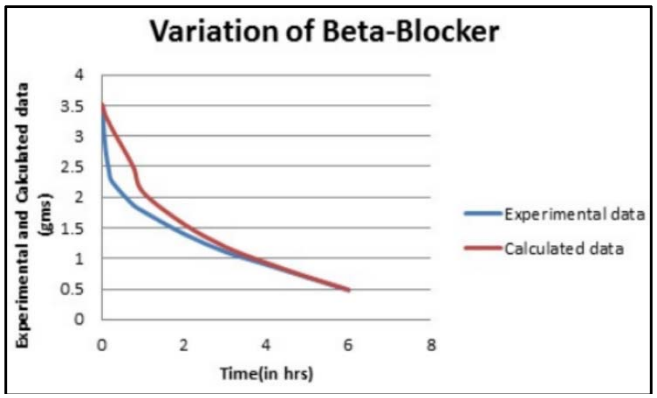


Fig 3

3.1.2 Picroside drug concentrations versus time curves

With the one-compartment model, if we continuously measure the concentration of a drug in the blood after an intravenous bolus dose and then plot these Purim concentrations against the times they are obtained, the curve shown in figure-3 would result. Note that this plot is a curve and that the blood concentration is highest just after the dose is administered, at time zero t_0. Because of cost limitations and patient convenience in clinical situations, only a small number of blood samples can usually be obtained for measuring drug concentration. From these known values, we are able to predict the purim drug concentrations for the times when we have no samples. In clinical situations, it is rare to collect more than two sample after a dose. In one experiment, the amount of Purim drug in the blood compartment at different times are found to be shown in table (3).

Table 3

Time (hrs)	Experimental data (gms)
0.00	36.0
0.5	25.018
1	18.038
2	14.158
3	11.318
4	8.96
8	3.50

using equation (3.1.1), (3.1.2) and (3.1.3) and find the value of b_{11}, λ_1,b_{12}, λ_2 by the method of exponential pealing demands sufficiently large values of t we neglect the points for which t is less than one hour. Here we take the amount in the first compartment is 36 gms and after solving we the value of b_{11}, λ_1, b_{12}, λ_2 is

b_{11} =24.41, b_{12} =11.59, λ_2 = -0.2400, λ_2 =-0.90

$y_1(t) = 24.41e^{-0.2400}(t) + 11.59e^{-0.90}(t)$

Using the above relation the value of y_1 at different times are found.

Table 4

Time (in hrs)	Experimental y1(t) (in gms)	Calculated y1 (t) (in gms)
0.00	36	36
0.5	25.018	29.04
1	18.038	23.914
2	14.158	17.02
3	11.318	12.661
4	8.96	9.663
8	3.50	3.58

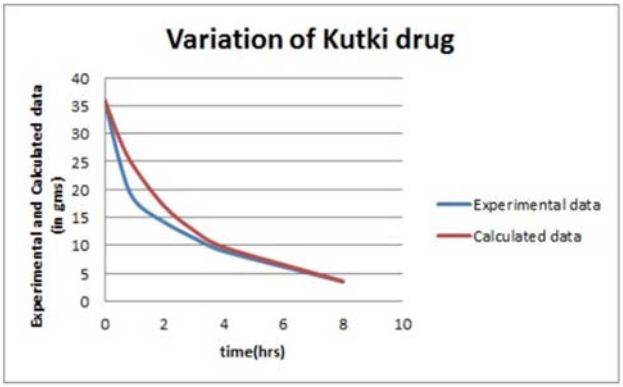


Fig 4

In one experiment, the amount of Picroside-1 in Purim drug in the blood compartment at different times are found to be shown in table (5).

Table 5

Time (in hrs)	Experimental y1 (t) (in gms)
0.00	0.9
0.5	0.725
1	0.455
2	0.359
3	0.283
4	0.223
8	0.087

using equation (3.1.1), (3.1.2) and (3.1.3) and find the value of b_{11}, λ_1,b_{12}, λ_2 by the method of exponential pealing demands sufficiently large values of t we neglect the points for which t is less than one hour. Here we take the amount in the first compartment is 0.9 gms and after solving we the value of b_{11}, λ_1, b_{12}, λ_2 is

$b_{11} = 0.85$, $b_{12} = 0.05$, $\lambda_1 = -0.256$, $\lambda_2 = -0.820$.
$y_1(t) = 0.85e^{-0.256}(t) + 0.05e^{-0.82}t$

Using the above relation the value of y_1 at different times are found.

Table 6

Time (in hrs)	Experimental y1(t) (in gms)	Calculated y1 (t) (in gms)
0.00	0.9	0.91
0.5	0.725	0.781
1	0.455	0.68
2	0.359	0.519
3	0.283	0.399
4	0.223	0.307
8	0.087	0.112

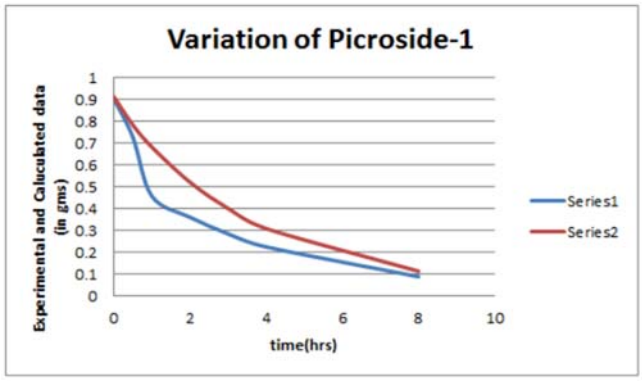


Fig 5

In one experiment, the amount of Picroside-2 in Kutki drug in the blood compartment at different times are found to be shown in table (7).

Table 7

Time(in hrs)	Experimental y1 (t)(in gms)
0.00	0.6
0.5	0.483
1	0.303
2	0.239
3	0.188
4	0.148
8	0.128

using equation (3.1.1), (3.1.2) and (3.1.3) and find the value of b_{11}, λ_1,b_{12}, λ_2 by the method of exponential pealing demands sufficiently large values of t we neglect the points for which t is less than one hour. Here we take the amount in the first compartment is 0.6 gms and after solving we the value of b_{11}, λ_1, b_{12}, λ_2 is

$b_{11} = 0.54$, $b_{11} = 0.06$, $\lambda_1 = -0.245$, $\lambda_2 = -0.79$
$y_1(t) = 0.54e^{-0.245}(t) + 0.06e^{-0.79}(t)$

Using the above relation the value of y_1 at different times are found.

Table 8

Time(in hrs)	Experimental y1 (t) (in gms)	Calculated y1 (t) (in gms)
0.00	0.6	0.62
0.5	0.483	0.518
1	0.303	0.450
2	0.239	0.343
3	0.188	0.265
4	0.148	0.205
8	0.076	0.112

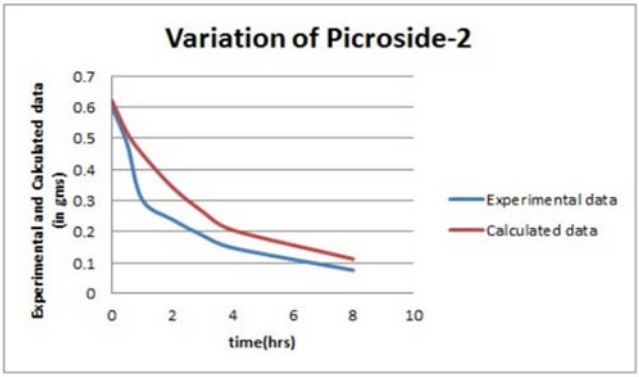


Fig 6

4. Conclusion

In the study of Mathematical model in herbal drug kutki kinetics we find that difference between the Experiment and the Calculate data in blood compartment is inversely proportional to time. Kutki root is well known for supporting liver function and for normalizing liver enzymes and also helps to cool the body and at the same time boost the immune system. It is contains very powerful anti-inflammatory agents such as apocynin which is great for treating arthritis and also to prevent blockages of arteries by platelets and thus prevent heart attacks. According to graph of variation of Beta-Blocker we conclude that the Calculated amount drug is maximum (33.5%) in comparision to Experimental amount of drug in blood compartment at time 0.75 hours. According to graph of variation of kutki we conclude that the Calculated amount of kutki drug is maximum (32.58%) in comparision to Experimental amount of drug in blood compartment at time first hours. According to graph of variation of Picroside-1 we conclude that the Calculated amount of picroside-1 is maximum (49.5%) in comparision to Experimental amount of drug in blood compartment at time first hours. According to graph of variation of Picroside-2 we conclude that the Calculated amount of pcroside-2 is maximum (48.5%) in comparision to Experimental amount of drug in blood compartment at time first hours.

5. References

1. Archer DR, Fowler HJ. Guide to Spatial and temporal variations in precipitation in the Upper Indus Basin, global teleconnections and hydrological implications. Hydrological and earth system Sciences 2004; 8:47-61.
2. Burn DH, Cunderlik JM, Pietroniro. Guide to Hydrological trends and variability in the Liard river basin. Hydrological Science Journal. A 2004; 49:53-67.
3. Dhar ON, Faroooqui. Guide to A study of rainfall at the Cherrapunji observatory, Hydrological science Bulletin 18, S.M.T., 1973.

4. Dhar ON, Kulkarni AK, Sangam RB. Guide to some aspects of winter and monsoon rainfall distribution over the Garhwal-Kumaon Himalayas-a brief appraisal, Himalayan Research & Development 1984; 2:10-19.
5. Dhar ON, Narayanan J. Guide to A study of precipitation distribution in the neighborhood of Mount Everest., Indian Journal of Meteorology and Geophysics. 1965; 16:230-240.
6. Dore MHI. Guide to Climate change and changes in global precipitation patterns: what do we know? Environmental International 2005; 31:1167-1181.
7. Douglas EM, Vogel RM, Knoll CN. Guide to Trends in flood and low flows in the United States: impact of spatial correlation. Journal of Hydrology. 2000; 240:90-105.