

# Research on Pharmacokinetics and Bioavailability of Coix-Seed Oil

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## Introduction

Coix-seed is dried seed obtained by removing the hard husk of the fruit of *coix* (*coix Lachryma-jobi L Var. Mayuen Stapf.*). It belongs to maze family and has been traditionally used as a drug for thousands of years. Over the years it has been reported overseas that coix-seed has significant inhibiting effects on ascites carcinoma and HCA solid carcinoma. Moreover it has been proven by pharmacodynamics that the effective anticarcinogen coix-seed oil, extracted from coix-seed through years of technological research, has the broad-spectrum effects in inhibiting and killing cancer cells to eliminating pathogenic factors and its intravenous preparation has been clinically administered and produced good curative effects on lung and hepatic carcinoma, etc. To further explore the internal process and mechanism of coix-seed oil preparation, coix-seed oil was labelled according to its structural characteristics with tritium. Through measuring the bioavailability and pharmacokinetics of various preparations administered in vivo, the absorption, distribution, excretion and metabolism of coix-seed oil were expounded so the rule of quantitative change plus other affecting factors has been understood. Furthermore the basis and conclusion of the hitech measuring method have been obtained and this experiment has built a pharmacokinetic foundation for the intravenous preparation of coix -seed oil to better guide clinical administration and provide a reliable foundation for the design and application of its oral preparation.

## Abstract

Pharmacodynamics, absorption, distribution, excretion and metabolism of coix-seed oil labelled with tritium were studied in normal rat. The intracorporal processes of <sup>3</sup>H-coix-seed oil administered through gastric perfusion and caudal intravenous injection into rat body were observed. Both processes abided by Open Two Compartment Model. The half-life for elimination was 14.23 hrs. for intravenous administration and 15.84 hrs for gastric perfusion. The percentage of bioavailability of gastric perfusion to that of intravenous injection was in AUC value as 62%. The <sup>3</sup>H-coix-seed oil injected into mouse body was widely distributed in every organ (mainly in liver and spleen). This provided a certain theoretic foundation for clinical administration. 40.6% of the drug were excreted through feces and 59.4% from urine. Total output for 24 hrs was 38.29% of the original injected drug. The plasma protein binding rate of <sup>3</sup>H-coix-seed oil was 98.4.

**Key Words:** <sup>3</sup>H-coix-seed oil, pharmacokinetics, bioavailability, histological distribution

## 1. Materials

### 1.1 Animals

Albino rats of series SD, 180±20g, fifty-fifty for male and female

Mice of Kunming species, 20±2g, fifty-fifty for male and female.

Supplier: Shanghai Research Institute of Pharmaceutical Industry

## 1.2 Main drugs and preparations

Coix-seed oil (supplied by KANGLAITE Pharmaceutical Co., Ltd., Batch No.: 96110, content: 99.75)

<sup>3</sup>H-coix-seed oil (labelled by Nuclear Institute of Chinese Academy of Science)

Soybean Lecithin (produced by Shanghai Pujiang Phospholipid Factory)

Tween-80 (pharmaceutically used)

70% perchloric acid, ether (AR), PPO xylene scintillator, POPOP scintillator, 30% H<sub>2</sub>O<sub>2</sub>, octanol (AR)

## 1.3 Instruments and Appliances

Microbalance, Beckman LS 9800 liquid scintillation counter (E>48%), high-speed homogenizer, scintillating glass bottle, syringe, egg-shaped bottle, GF-silica-gel-plate, dissection appliances, radiation protection appliances, etc.

## 2. Methods

### 2.1 Preparation of intravenous <sup>3</sup>H-coix-seed oil

The mixture of <sup>3</sup>H-coix-seed oil, soybean phospholipid, glycerin and distilled water was homogenized into an even emulsion under 80 °C constant temperature bath with high-speed homogenizer. Then the emulsion was sieved and poured into a container and sterilized by steam and measured for its radioactive intensity.

### 2.2 Preparation of oral <sup>3</sup>H-coix-seed oil

<sup>3</sup>H-coix-seed oil was diluted and evenly mixed with distilled water and Tween-80 and was measured for its radioactive intensity.

### 2.3 Preparation of biological samples

#### 2.3.1 Blood sample

Blood (0.1ml) was sampled from the sockets rat and mouse into test tubes. Heparin was added as anticoagulant and then 70% of perchloric acid (0.5ml) and 30% H<sub>2</sub>O<sub>2</sub> (0.1mg) were respectively added. The samples were digested in the constant 80°C bath for 30 minutes. Then distilled water was added until the sample volume reached 1 ml and posterior to being shaken 0.1 ml of the sample was put into a scintillating bottle to be measured.

#### 2.3.2 Histological sample

The mouse was killed by breaking its cervical vertebrae. Its internal organs were rinsed with physiological saline and then blotted with filter paper. 100mg of each organ was removed as a sample. 70 % of perchloric acid (0.5ml), 30% H<sub>2</sub>O<sub>2</sub> (0.1ml) and 1 drop of octanol were respectively added. The sample was digested in the constant 80°C bath for 60 minutes before it was cooled. Then distilled water was added until the sample volume reached 1ml and posterior to being shaken, 0.1ml of the sample was put into a scintillating bottle to be measured.

### 2.3.3 Feces and urine samples

Feces sample (100mg) and urine sample (0.1ml) taken in different periods were precisely measured. 70% of perchloric acid (0.5ml), 30% H<sub>2</sub>O<sub>2</sub> (0.1ml) and 4 drops of octanol were respectively added into the samples. The samples were digested in 80°C constant temperature bath for 60 minutes. Then distilled water was added until the sample volume reached 5ml and 0.1ml of the sample was put into a scintillating bottle to be measured.

### 2.3.4 Radiation measurement

After the digested sample (0.1ml) was put into a scintillating bottle, PPO xylene scintillater (5ml) was added. Its radioactivity was measured with liquid scintillation counter.

### 2.3.5 Data processing

All data underwent curve-fitting with 39-87 pharmacokinetics software by using residual-number method and simple-shape accelerating method and got measured according to the rule of minimal AIC estimation.

## 3. Results

### 3.1 Comparison of bioavailability of <sup>3</sup>H-coix-seed oil intravenous preparation and oral <sup>3</sup>H-coix-seed oil preparation

12 rats, both male and female, were randomly divided into 2 groups (6 rats a group). After weighed before experiment they were made to fast on water for 24 hr. The 2 groups of rats were administered respectively with <sup>3</sup>H-coix-seed oil emulsion (0.5ml, 0.25g/kg) through the caudal intravenous injection and through gastric perfusion respectively. 1, 10, 30, 60, 120, 240, 480, 720, 1440 minutes posterior to administration blood (0.1 ml) was sampled from the rat sockets. After the blood-samples were digested their radioactivity was measured to obtain AUC value.

AUC:

0-----T[n]

AUC = oral administration/intravenous administration

0-T = 3941.83μg/6357.8μg=61.9%

0-----Infinite

AUC= oral administration/intravenous administration

0-- 5016.5342μg/8077.5273μg =62.1%

### 3.2 Drug concentration and pharmacokinetic parameters of the <sup>3</sup>H-coix-seed oil preparation for single intravenous injection

18 rats of Series SD were evenly and randomly divided into 3 groups. The 3 groups of the rates were administered respectively with <sup>3</sup>H-coix-seed oil preparations (0.25g/kg, 0.125g/kg and 0.0625g/kg) through the caudal intravenous infection respectively. 0.0167, 0.167, 0.5, 1, 2, 4, 8, 12, 24 hr posterior to administration, blood (0.1ml) was sampled from the rat sockets. After the blood-samples were digested, their pharmacokinetic parameters were measured and

calculated.

Table 1. Measurement result of rat drug concentration of the intravenous injection at different dosage and different time

Measured value(mg)	Time (hr)								
	0.0167	0.17	0.5	1	2	4	8	12	24
Big dosage	1872.3	955.0	404.3	320.6	238.3	192.6	172.1	145.0	109.0
Medium dosage	1003.4	594.0	258.6	216.8	188.9	162.9	128.4	104.0	74.9
Small dosage	595.5	379.5	157.1	119.8	103.4	80.3	65.7	50.6	38.5

Table 2. Pharmacokinetic parameters of intravenous <sup>3</sup>H-coix-seed oil preparation of the rats

Parameter	Dosage(g/kg)		
	Big	Medium	Small
A (μg)	1730	879.8	533
α (1/h)	5.1	4.9	4.2
B (μg)	263.32	200.4	104.6
β (1/h)	0.04375	0.046	0.049
tα/2 (hr)	0.135	0.141	0.166
tβ/2 (hr)	15.84	15.80	15.91
K21 (1/h)	0.71	0.94	0.727
K10 (1/h)	0.31	0.24	0.286
K12 (1/h)	4.12	3.75	3.21
AUC (μg)*hr	6357.8	4459.14	2229.2

### 3.3 Drug concentration and pharmacokinetic parameters of the oral <sup>3</sup>H-coix-seed oil preparation for single administration

18 rats of Series SD were evenly and randomly divided into 3 groups. The 3 groups of the rates were administered respectively with oral <sup>3</sup>H-coix-seed oil preparations (0.25g/kg, 0.125g/kg and 0.0625g/kg) through gastric perfusion. Respectively 0.0167, 0.167, 0.5, 1, 2, 4, 8, 12, 24 hours posterior to administration blood (0.1 ml) was sampled from the rat sockets. After the blood samples were digested their pharmacokinetic parameters were measured and calculated.

Table 3. Measurement result of rat drug concentration of the oral administration at different dosage and different time

Measured value ( $\mu\text{g}$ )	Time (hr)								
	0.0167	0.17	0.5	1	2	4	8	12	24
Big dosage	6.4	19.2	32.3	84.6	234.5	373.7	248.6	205.3	151.8
Medium dosage	3.3	18.2	27.0	70.6	200.1	282.4	219.9	161.4	114.4
Small dosage	1.5	3.1	18.0	64.4	138.3	210.0	151.4	125.7	84.8

Table 4. Pharmacokinetic parameters of oral  $^3\text{H}$ -coix-seed oil preparation of the rats

Parameter	Dosage(g/kg)		
	Big	Medium	Small
A ( $\mu\text{g}$ )	33.75	29.62	20.72
$\alpha$ (1/h)	2.29	2.87	3.54
B ( $\mu\text{g}$ )	421.7	308	235.7
$\beta$ (1/h)	0.05	0.04	0.04
$t_{\alpha/2}$ (hr)	0.30	0.24	0.215
$t_{\beta/2}$ (hr)	14.47	14.88	14.23
$t_{\alpha K/2}$ (hr)	1.18	0.94	1.08
K <sub>21</sub> (1/h)	1.83	2.22	2.9
K <sub>10</sub> (1/h)	0.06	0.05	0.05
K <sub>12</sub> (1/h)	0.44	0.64	0.62
AUC ( $\mu\text{g}$ )*h	6372.78	5477.62	3941.83
CL (s)	0.00013	0.00008	0.0005
T <sub>peak</sub> (hr)	4.96	4.86	4.76
C <sub>max</sub> ( $\mu\text{g}$ )	306.46	242.26	178.35

#### 3.4 Histological distribution of intracorporal $^3\text{H}$ -coix-seed oil preparation for single intravenous injection

54 mice of Kunming species were evenly and randomly divided into 9 group (6 mice a group). The mice were administered with  $^3\text{H}$ -coix-seed oil preparations (0.25g/kg) through caudal intravenous infection. 0.0167, 0.167, 0.5, 1, 2, 4, 8,12, 24 hr posterior to administration the 9 groups of mice were respectively killed. For each mouse about 100 mg of its tissues of blood, liver, spleen, kidney, lung, stomach, brain and intestine were removed with dissection. After the mixture of the tissues was precisely measured and digested its content of radioactive material was measured and calculated.

#### 3.5 Excretion

5 mice of Kunming species were respectively put into 5 metabolic cages. The mice were administered with <sup>3</sup>H-coix-seed-oil preparations (0.25g/kg) through the caudal intravenous injection. For each mouse 0.1ml of a urine sample and 100mg of a mixed feces sample were regularly collected at different period and digested. Then scintillater was added to measure radioactive intensity at the periods of 0-4hr, 4-8hr, 8-12hr and 12-24 hr.

Table 5.

Item	Time				Total
	0-4hr	4-8hr	8-12hr	12-24hr	
Urine (μg)	945±328	497±10	373±83	460±136	2275
Feces (μg)	464±150	339±22	311±193	440±198	1554

\* Total excretion: 2275μg+1554μg=3829μg

∴ Every mouse was injected with 10mg

∴ The percentage of excreted quantities to the total injected quantities:  
3829mg/10mg=38.29% including 59.4% of urine and 40.6 of feces

Table 6.

Time (hr)	Urine and feces				Accumulated %
	%	Accumulated %	%	Accumulated %	
4	9.45	9.45	4.64	4.64	14.09
8	4.97	14.42	3.39	8.03	22.45
12	3.73	18.15	3.11	11.14	29.29
24	4.60	22.75	4.40	15.54	38.29

\*:The data in the table showed the percentage of excreted quantities to the injected dosage.

### 3.6 Plasma protein binding rate

#### 3.6.1 In vitro

After <sup>3</sup>H-coix-seed oil (50μl) and 30%TCA were sequentially added in the blood-sample (1ml) which was sampled from a normal untreated mouse, the mixture was centrifuged, precipitated and supernate and precipitate were respectively measured for radioactivity. Mean value of radioactivity reading: supernate: 5515; precipitate: 340765. binding rate: 340765/340765+5515×100%=98.4%

#### 3.6.2 In vivo

<sup>3</sup>H-coix-seed oil of the same batch as that in 3.6.1 was administered to each mouse. 4 hours later blood was sampled and 30% TCA was added. The mixture was centrifuged, precipitated and supernate and precipitate were respectively measured for radioactivity. Mean value of radioactivity reading: supernate: 2547, precipitate: 10523, binding rate: 10523/2347+10523×100%=80.5%

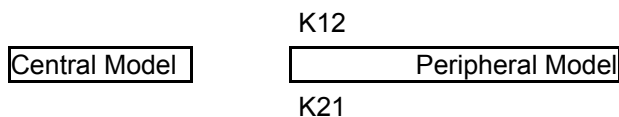
## 4. Discussion

### 4.1 Selection of measuring method

Coix-seed oil has very effective curative action against cancer. To study its drug metabolism and absorption properties, radioactive isotope was selected as its tracer. Excessive tritiums were added to label all the double bonds i.e. those of unsaturated fatty acids. The labelled component not only has the original physical and chemical properties but also has the properties of radioactive nuclein. So its movement and locations in the body can be detected. Because nuclein has the same chemical and biological properties as those of relevant common atoms and molecules in nature its chemical changes in the body are the same as those of biological process. The following are the properties of radioactive  $^3\text{H}$ -labelling: (a). It has high sensitivity and is 10 times more sensitive than the most sensitive analytical balance. (b). It produces negligible interference and intracorporal metabolites only have small interfering effects. So the movement and transformation of a drug in extremely small dosage can be quickly and precisely detected. (c) It is easy to operate for it is not necessary to separate the labelled drug to be measured from biological samples in this measuring method. (d). It can distinguish between exogenous drugs and endogenous drugs. Some drugs are also normal metabolite in the body so the  $^3\text{H}$ -labelling method is the unique suitable measuring method. (e). It is compatible to the conditions in the body. Previously because some measuring methods were not sensitive enough, more often than not, excessive pharmaceutical dosage which was often toxic was needed to measure drugs. In this situation normal physiological functions are disturbed so the measuring result can not show the drug metabolism under normal physiological conditions. Nevertheless because the radioactive isotope has high sensitivity, it can be used to study metabolism process in the dosage the same as or less than the curative dosage. (f). The distribution of tracers can be observed with radiography. The reason why  $^3\text{H}$  was selected as a tracer is that organic chemical compound contain hydrogen so if  $^3\text{H}$  is used to permute hydrogen, the properties of organic chemical compound would not be affected. Moreover there is an abundance of  $^3\text{H}$  which is inexpensive and whose labelling procedure is simple and energy of radioactive ray is low. Furthermore it can evenly be distributed in the body and its toxicity is the lowest compared with other isotopes. Consequently the radioactive  $^3\text{H}$  was used to label coix-seed oil.

### 4.2 Research on pharmacokinetics

Under normal conditions after a drug is absorbed, it would be distributed with blood circulation to every tissue in the whole body. The drug in tissues and their metabolites would be transported to excreting organ and be excreted at last. So the drug concentration in blood virtually shows the state of the metabolism processes of absorption, distribution and excretion etc. According to measurement the pharmacokinetics models of intravenous  $^3\text{H}$ -coix-seed oil preparation and oral  $^3\text{H}$ -coix-seed oil preparation were both fitted for Open Two Compartment Model:



Through analyzing pharmacokinetic parameters of intravenous <sup>3</sup>H-coix-seed oil preparations of 3 dosage (big, medium, small), it was observed that there was no significant difference among the parameters. The absorbing half-life ( $t_{1/2}$ ) was only 0.135 hr and the eliminating half-life ( $t_{1/2}$ ) was 16 hr. Obviously the drug administered with intravenous injection could be quickly absorbed, distributed and quickly produce curative effects in the body. The drug was slowly eliminated from blood and its curative effects could remain for a relatively long time. Through analyzing pharmacokinetic parameters of oral <sup>3</sup>H-coix-seed oil preparations of 3 dosage (big, medium, small), it was also observed that there was no significant difference among the parameters and the absorbing half-life was 0.3 hr and the eliminating half-life was 14 hr. Obviously the drug orally administered underwent a relatively long drug metabolism and was not easy to be eliminated. In light of characteristics of the half-life and the possibility of drug accumulation resulted from long-term administration, it was advised that initially certain loading dosage was administered posterior to a certain interval maintaining dosage was administered.

Time-effect curve of both intravenous and oral administration showed a slowly declining curve which was related to the slow drug releasing ability of cells in tissues of each organ.

#### 4.3 Bioavailability

The two pharmaceutical preparations having identical chemical properties did not mean that they had identical biological effects. Oral <sup>3</sup>H-coix-seed oil preparation was in developing stage so it was important to compare it with the intravenous preparations clinically proven effective.

According to AUC value (area under curve) of the time-effect curve of intravenous administration and oral administration under the dosage, the relative bioavailability of the oral preparation to that of intravenous preparation was 62%. In terms of clinical requirement, the oral preparation which had advantage of being easy to carry and convenient to administer, was practical. Nevertheless AUC value only showed the total absorbed quantities of single administration. According to measurement the peak drug concentration ( $C_{max}$ ) of the oral preparations with big, medium and small dosage was respectively 306.46mg, 242.26 $\mu$ g and 178.36mg and the peak time was respectively 4.96 hr, 4.86hr and 4.76 hr.

Both peak drug concentration and peak time are good indexes for drug-absorbing rate. Clinical dosage and time of administration for drug can be determined by these two peak values in the design of clinical drug.

#### 4.4 Histological distribution

Drug distribution in each organ posterior to intravenous injection for mouse at different time



showed that this drug had high affinity for tissues and its persistent period was long. 10 minutes posterior to administration the radioactive intensity in liver, spleen, etc. was much higher than that in blood and slow in elimination. This phenomenon supported the view that the concentrated distribution of this intravenous emulsion drug in certain organs was resulted from the action of phagocytizing and retaining oil-drop by phagocytes in reticuloendothelia system. It also supported the clinical observation that this drug had significant curative effects on lung, hepatic and kidney carcinoma. The drug content in stomach was lower than that in above-mentioned organs. But its persistent-period was long and if a subject was administered many times in long-term with this drug considerable quantities would be accumulated in the stomach. Consequently this drug also had clinical curative effects on stomach cancer. The drug concentration in brain was relatively constant and this showed that it could penetrate blood brain barrier to produce curative effects. Whether this phenomenon was related to anodyne effect remained to further experiment. Drug concentration in kidney was the highest 0.5 hr posterior to administration and then it sharply declined. Initially drug concentration in intestine was low but with the lapse of time it was elevated. This might be resulted from enterohepatic circulation.

#### 4.5 Excretion

The excreting state of labelled drug in urine and feces was observed. The percentage of the excreted quantities to the injected dosage was only 38% 24 hr posterior to administration. This showed that this intravenous preparation was slow to excrete. The possible reasons that it was excreted with bile or through other ways or it was accumulated among the contents of stomach and intestine remained to be proven after further experiments.

#### 4.6 Plasma protein binding rate

The binding of drug with plasma protein is reversible. It affects not only pharmacokinetics but also action intensity and persistent period of the drug. Moreover it is often closely related to action mechanism and interacting effects, etc. of the drug. In this experiment 4 hr posterior to administration the binding rate of <sup>3</sup>H-coix-seed oil with plasma protein was 80%. This drug also had strong affinity with other tissues. In short the binding rate of <sup>3</sup>H-coix-seed oil with plasma protein was high than that of other drugs. So both its action period and eliminating half-life were high.

#### 4.7 Relation of channel tropism theory to conclusion of this experiment

Traditional Chinese Medicine holds that *coix* seed tastes sweet and is cold-natured and is distributed to the channels of spleen, stomach and lung. Though the organs described in the theory of viscera and channels of Traditional Chinese Medicine are not completely identical with those of Western medicine, at least the main functions of both are equal or similar. Moreover the traditional effects of *coix* seed are similar to those held by modern pharmacology. It is held in Traditional Chinese Medicine that channel tropism is the oriented distribution of the drug to a certain part of the body i.e. the drug is oriented to the part of the

body where it is to take effect. Furthermore channel tropism is a comprehensive concept of space and function based on the theories of channel, viscera and phase. The selectively distributing characteristics of effective components of Chinese herb in vivo are held as the material foundation for channel tropism and can yield clues for expounding the essence of channel tropism. Researches show that 61% organs belonging to channel tropism of the drug are practically identical to the organs which accumulate the biggest quantities of effective components. Consequently the selectively distributing characteristics of effective components of Chinese herb in vivo are the major foundation for channel tropism.

The result of this experiment showed that the main effective components of *coix*-seed were distributed to the organs of spleen, liver and lung which was somewhat different from those of channel tropism.

Nevertheless this experiment had provided a modern scientific foundation for traditional channel tropism theory of *coix*-seed property and relevant researches and made an exploration for the method and direction of experimental research on the property of traditional Chinese herb medicine.

Clinical practice and pharmaceutical research showed the preparations made from chemically equal drugs often produced some biologically unequal effects. Consequently it was imperative to study bioavailability and pharmacokinetics, to design preparations and production processes and to guide clinical dosage and administration methods on hi-tech basis in developing stage of new drugs.

Components of Chinese herb medicine are very complicated. From the angle of pharmacodynamics most researchers lay emphasis on studying its effective components in the past few years. Because Chinese herbal medicine is traditionally administered by experience and there is short of quantitative observance on its absorption, metabolism, etc. in vivo, the pharmacokinetic researches on Chinese herb medicine has been listed as a new research direction. <sup>3</sup>H-labelling method has provided a simple and sensitive research method on studying the absorption, distribution, excretion and metabolism of the effective components of Chinese herb medicine. This experiment had made some initiative explorations on pharmacokinetics of the Chinese herbal medicine with complicated structure and provided some quantitative indexes for the intracorporal process of *coix*-seed so as to provide new developing direction for this long-history traditional Chinese herbal medicine and further make the present clinical preparation of this drug more practical and perfect.

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