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Study Title: Pharmacokinetics Study of Antitumor B in Healthy Volunteers
This study is approved by IRB protocol STUDY00001235

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Antitumor B (ATB), also known as Zeng Sheng Ping, is a Chinese herbal mixture composed of six plants: *Sophora tonkinensis*, *Polygonum bistorta*, *Prunella vulgaris, Sonchus brachyotus, Dictamnus dasycarpus,* and *Dioscorea bulbifera* (Table 1). ATB is available as 300 mg tablets and has been traditionally used in China for dysplasia (dose 4-8 tables/ twice daily). Several studies in rodents and humans have been published demonstrating the chemopreventive activity of ATB against various cancers (e.g. lung, esophageal and oral) (1-6). ATB appears to be very effective in the chemoprevention of upper aerodigestive tract tumors in humans and also safe to several thousand subjects over a period of more than two decades (2-4). Therefore, we believe that a single dose of administration of anti-tumor B using 4 tablets are going to be safe in human.

Table 1. Composition of Antitumor B (percent weight)

Herbal Name		Form	% Content
Latin	Chinese		
Sophora tonkinensis	Shan Dou Gen	Water Extract	18-24
Polygonum bistorta	Quan Shen	Water Extract	17-21
Prunella vulgaris	Xia Ku Cao	Water Extract	18-25
Sonchus brachyotus	Bei Bai Jiang	Water Extract	17-23
Dioscorea bulbifera	Huang Yao Zi	Water Extract	3-6
Dictamnus dasycarpus	Bai Xian Pi	Powder	8-12

However, we currently do not know if pharmacologically relevant concentrations can even be achieved at the site of action (oral) for the chemopreventive action. We are interested in doing a human single-dose (8 tablets once) full pharmacokinetic study of ATB. We plan to collect 9 blood (1-2 mL each) and 9 saliva samples (1-2 mL each) from 10 healthy volunteers over a period of 24 hrs (at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hrs) to

1) determine the saliva and plasma concentration of four key constituents of ATB and
2) develop the *in vivo* correlation between plasma and saliva concentrations.

We will procure the tablet for the human study from the GMP manufacturing facility at National Engineering and Research Center for TCM Shanghai Traditional Chinese Medicine Technology Co. Ltd. (Shanghai, China).

1.0 Procedures Involved

A maximum of 50 subjects will be enrolled in the study after signing the consent form. Health questionnaire and blood biochemistry[1,3], and HIV, Hepatitis B and C tests will be used for screening for all inclusion/exclusion criteria and selecting the subjects for drug administration. The first 8 participants to meet exclusion/inclusion criteria will be finalized as volunteers and invited to take part in rest of the study. The selected subjects will be given water 30 mins before the administration of dietary supplement to promote saliva production. 2400 mg of ATB (8 tablets of 300 mg each) will be administered to each subject and 9 blood and saliva samples[2] (pre-dose, 0.5, 1, 2, 3, 4, 6, 8 and 24 hrs) will be collected from each subject. Subject will drink water 30 mins before each sample point to promote saliva production.

The blood sample for biochemistry analysis[3] will also be collected after 24-hr sample point from each subject. The specimens (blood and saliva samples) will be analyzed for fraxinellone, dictamnine, maackiain and matrine concentration, and blood-saliva concentration correlation and PBPK model will be generated using PK modeling software.

Out of 8 selected participants, 2 subjects (randomly selected) will be administered with the herbal supplement in round 1 of the study on a particular day to ensure all the processes related to study (saline lock insertion[3], administration of substance, saliva and blood sample collection and providing adequate emergency care in case of any unforeseen/unexpected event) are conducted smoothly and processes flow can be modified/adjusted before rest of the 6 subjects are administered with the herbal supplement in round 2. There is no difference in either the drug administration or any research procedures between round 1 and round 2. The study is done in two rounds just to ensure study volunteers' ease and safety during various study processes.

Note: [1]Participants need to fast for 8-12 hrs before blood draw for biochemistry test (both for screening and post-study). [2] Participants need to avoid any drink 15 mins before each saliva sample. [3] UH Health center will stop the blood draw procedure, if the vein cannot be located in three attempts. The study team will discuss with participants if they would like to continue with the study. The participant then will be requested to come back another day, if they are still interested in continuing with the study. After 3 unsuccessful attempt a second time, participant will be removed from the study at the discretion of study team.

2.0 Risks to Subjects

We are not anticipating any side-effects due to single-dose administration of ATB. Study participants will have a saline lock inserted by the UH Student Health Center, in order to avoid repeated needle inserting. Potential risks associated with a saline lock include pain during the insertion process, infiltration during the infusion of saline prior to, or after the blood draw and phlebitis (inflamed vein). A bruise (a black and blue mark, redness, or pain) might form at the location where the saline lock needle was inserted. Phlebitis risk is minimal as the saline lock duration is less than 8 hours. If the saline lock becomes infiltrated during flushing, the lock will be *removed,* and warm compresses applied.

Total blood volume will be drawn in 24 hours: 12 mL x 9 samples = 108 mL. A healthy person can donate 450 mL ± 10% blood at once (The Joint United Kingdom Blood Transfusion and Tissue transplantation Service Professional Advisory Committee). 10 mL Blood will be discarded at each sample point and 2 mL will be collected for sample analysis at the designated time points. After 8 hours, the saline lock will be removed. 24 hour time point samples are collected with needle and syringe. Some people may have a lightheaded or dizzy feeling; an upset stomach; fainting or loss

of consciousness and injury from related falls; or very rarely, nerve or artery damage due to blood withdrawal.

In some rare instances, people could experience allergic reaction, mild diarrhea and nausea as a result of ATB administration.

3.0 Costs/Payments to Subjects

Subject will be responsible for loss of pay, if any, due to the participation in the study and the cost of conveyance to reach the site of study for each and all required blood samplings.

In case of any unexpected event or emergency, if any emergency medical treatment (including ambulance service) is required and given either by the UH health Center or any other service provider, the cost will not be covered by the study but by the participants' insurance.

Describe the amount and timing of any payments or inducements to subjects.

$360 worth of gift card(s) will be paid as compensation to each subject upon commencement of the study.

Indicate if subjects will need to complete all measures/procedures prior to receiving any remuneration, or if the payment will be pro-rated.

After the conclusion of study, we will provide one $25 gift card for each first 6 time points, and $45 gift cards each for 6 and 8 hr time points for the blood and saliva samples collected from the subject, even if the subject does not complete the study.

References:

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