

Professional Help

-Contact with Local Pharmaceutical Companies

In order to get a clearer picture of UDCA-contained drug's manufacturing circumstance in China, our team visited Tianjin Pacific Chemical & Pharmaceutical Company to interview the experts about current chemical producing methods. According to Mr. Xing Ruwen and Mr. Li Jinlong, the most popular method of producing UDCA-contained medicine in the market mainly focuses on chemical pharmaceutical procedures. Yet this approach has disadvantages including relatively weak efficacy and potential harm to health of the workers. He praises our aim to produce UDCA medic in biopharmaceutical procedure and consider it very promising. Furthermore, he encouraged us to cut off cost so that our method can be accepted by the market and the patients. This suggestion helped us to clarify our future goal.



Mr. Xing Ruwen is the chief engineer in Tianjin Pacific Chemical & Pharmaceutical Company. He is an experienced manager who has been working on Chemical method of producing UDCA-contained drugs for years.

Mr. Xing introduces us the traditional chemical procedure to manufacture the UDCA-contained drug. Also, he leads us to visit the processing workshop and teaches us many valuable knowledge about drug production.

According to his opinion, chemical method of producing UDCA-contained drug basically has two disadvantages: the first one is its high risk; the second one is related to profit, a factor that influences manufacturing the most. For its potential high risk, Mr.

Xing conveys that it comes from the utilization of metal sodium. Sodium is well-known for its highly-reactiveness; it is able react violently with water, which at the same time release large amount of heat and might cause potential safety issue to the workers. He praises our thought of avoiding the dangerousness and very much acknowledges our method.



Mr. Li Jinlong works as the production manager and he also participating in marketing department's work in Tianjin Pacific Chemical & Pharmaceutical Company.

Mr. Li patiently answers our questions related to marketing. Analyzing its cost, demand and also profit, Mr. Li helps us to determined our minds on trying to solve the problem step by step. He informs that currently the successful UDCA synthesis rate is not hight enough and requires repeating measures to increase its purification ratio. It is very important for us to consider more about the balance between cost and profits if we want to further develop our method. Now, the exported UDCA drugs are highly demanded and we need to find ways to help simplify the production process and to increase the supply of UDCA-contained drugs.

Q: We still have some questions regarding to the market. It would be such a pleasure if you can share some of your ideas or understandings about them.

A : Please ask, I'm very glad to help you.

Q1: Could you please inform us UDCA medicine's value in market and its efficacy?

A: UDCA is an cholic acid medicine that has choloretic effect to human bodies. It can cure various dan diseases like gallstone as well as hepatopathy including hepatic adipose infiltration. UDCA medicine has stronger healing effect than CDCA

medicine while having less side effects in treatment. However, subtracted from bears, UDCA has a relatively high costs. And using UDCA directly converted by CDCA mainly has two benefits: first of all, it requires a lower cost because CDCA is subtracted from poultry like chickens, ducks, and geese; also, use CDCA instead of UDCA can help protect wild animals (bears.) Also, I consulted experts in our marketing department about it and they revealed to me that this approach has very high vendibility that medicines manufactured oversea are in short supply.

Q2: What is the basic principle of this drug design/production?

A: First we extract CDCA from the bile of chicken, duck and geese. Then we convert CDCA into UDCA through two steps of redox reaction. These two substance are isomers than differ in their three-dimensional structure only.

Q3: We found out that there are only few factories manufactures UDCA medicine. Is it because the producing process's complexity? Where is the complexity embodied in specific?

A: In fact, the actual process or technology used is not very complex but the key dangerous factor is the need of sodium, a dangerous, active metal that burns when it meets with water. Moreover, to consider this issue from other perspectives, UDCA medicine's production copes with the pressure from people's safety and environment protection concerns. Therefore there are not too many factories that manufactures UDCA medicine.

Maybe there are only two factories in China that manufactures this active pharmaceutical ingredient (API) officially; one is in Shenzhen and the other is in Suzhou.

.....After biliary drainage, it is very likely that bears will suffer from diseases all over their body, which is a torture to them. To resolve this problem, researchers and scientists in our country wish to convert CDCA in order to receive UDCA. Currently, their methods are deeply restrained by the use of sodium due to its danger and difficulty. If you can convert CDCA to UDCA successfully using enzymes, you are making a huge contribution.

Also, there are a lot of problems in the production of UDCA in medical industry. For instance, we need to consider the safety and profits of this drug. Thus, there are still a lot of aspects need to be considered and experiments need to be done when involved in industrial production.

Q: Thank you for your suggestions.

Q4: Could you briefly introduce the issue concerning costs and profits?

A: It is complicated because hydrogen needs to be removed. The chemical composition of UDCA needs to be refined repeatedly, which is tricky. For example, a concentration of 70% of UDCA? require three times of refinement at least in order to reach the standard. Also, the raw materials or substances need to be recollected and there will be turnovers and other complex factors during the process. So the profits is limited. And now the biggest issue is that the danger of production overweights its potential profits.

-Contact with scientists regarding specific technological issues/ suggestions



Prof. Xu Jianhe is a well-respected professor in Biocatalysis and Bioprocessing State Key Laboratory of Bioreactor Engineering in East China University of Science and Technology.

With many questions regarding to complex bioprocessing and enzyme catalysis, we write to Prof. Xu, a very famous professor in China and also expert to get further instructions and professional help. At the beginning of our experiment, we decided to employ a two enzyme in one pot catalyzed reaction(see figure.1). However, after our initial attempt, we found out that the reverse reaction was more prevalent than the forward reaction. Thus because of this, the product was actually CDCA, the initial reactant, instead of UDCA, our expected product. This conundrum stopped us from reaching any further into the experiment. At this time, Prof. Xu suggested us to separate the two enzymes into two steps. (see figure 2) After listening to his suggestion, our team worked together and produced our new experiment plan with a two step reaction instead of one. In this way, the end product will not be transformed back into CDCA, and the mass production of USCA proves to be successful. As well as enhancing the

biopharmaceutical effect of UDCA, we also aims to reduce the production cost. When we were designing the experiment, we included the usage of cofactors: NADH and NADP⁺. However, the cost of cofactors can be immense if they are not regenerated. After hearing about our problem, Prof. Xu suggested us finding enzymes to help with the regeneration of cofactors. With his suggestion in mind, we eventually employed GDH(Glutamate Dehydrogenase) to regenerate the cofactor NADP⁺, and LDH(Lactate Dehydrogenase) to regenerate the cofactor NADH. Carefully answering our questions and giving us other valuable information and cases about our topic, Prof. Xu used his actions to encourage us in refining our experiment and to give it a try.

Figure 1:

Figure 2:

Outreach

-Contact with Local Hospital and Patients

In addition, we contact local patients from Xuanwu hospital who suffered from liver cirrhosis to discuss the curing effects and prices of various UDCA-contained medicines in the market to determine our direction. Through our interviews, we understood that current UDCA medicines in the market are unaffordable for patients with average or below average income in long term treatment. Also, medicine which price can be accepted by the patients has relatively weak curing effect. In order to solve this problem, we consulted experts from doctors from Xuanwu Hospital. She reported that UDCA has a large pharmaceutical application. As well as UDCA's usage in dissolving gallstone, its efficacy in primary biliary cirrhosis and primary sclerosing cholangitis (PSC) as an adjunct to medical therapy has been well established. Newer indications include its use in the management of chronic hepatitis, cirrhosis, post liver transplant rejection, graft-versus-host disease and acute viral hepatitis, where it not only relieves symptoms of cholestasis but also arrests ongoing hepatocyte necrosis.

Patients interview:

Q: Hi, how are you Mrs. Zhou?

A: Good, good. I'm feeling much better now.

Q: If it's possible, can you briefly explain to us what exactly are you suffering from?

A: Ahh. It's not a problem. Well, I've been diagnosed with liver cirrhosis for several years now. And I've been constantly taking medicine to treat it. It costs a lot of money. Too expensive!

Q: What is this medicine that you are taking now that is this expensive?

A: I don't really know the exact name, but you can have a look at it. It's a medicine produced in America.

Q: Oh? America? Why aren't you taking any of the medicine produced locally.

A: That's a long story to tell. This medicine I'm taking is supposed to be composed of UDCA. From what the doctors told me, this medicine is designed to treat diseases like what I have here. But it seems like only the America version works on my. The locally produced version of this medicine is chemically synthesized so I guess it's not really a good thing. And I can feel it too. Because my stomach often hurts from taking the medicine.

Q: Wait... Are you sure of it? Are you sure that your pain comes from taking the chemically synthesized medicine?

A: Well yes. The pain usually starts an hour or half after taking the medicine. And the doctors confirmed my theory as well. They say this chemically synthesized version of the medicine would usually have gastrointestinal discomfort as a side effect.

Q: Well that's not good! So have you considered any other choices? Or have the doctors recommended anything else?

A: Yes. And that's actually why I'm telling you how expensive the medicine is. The chemically synthesized version of this medicine is not that expensive. Although it cannot be covered by medical insurance. It's definitely affordable. The medicine I'm taking now is indeed very good. It doesn't have any side effects. I guess the only side effects is that it is too expensive. I can't really afford it now. I really want an alternative. But it sees like the only alternative is bear bile powder.

Q: What do you know about bear bile powder?

A: I know it's not extremely expensive so I can probably afford it. But I also know how people acquire bear bile powder. Ugh, I don't want to cause that much pain to the poor bears. They say no trading, no killing right? So that's not really an option for me.

Q: Yeah. It is indeed very brutal. Well, thanks for your time Mrs. Zhou. We really appreciate your help.

A: No problem! Have a good day.

Q: You too.

-Contact with Chengdu Bear Rescue Centre



To find out more about the bear bile industry and the protective measures against illegal hunting, our team, SDSZ-China, went all the way down south to Sichuan province, where the biggest Asiatic Black Bear rescue centre is located. There, after exchanging conversations with the staff, we found out that Asiatic Black Bear is listed as endangered on the IUCN red list, and the most efficient way to rescue bears now is buying bile bears from bear farms. (Since bear farming is a legal activity in China, there's no way to officially put a halt on this). After this trip, we went a bit west and visited a real bear farm where bile is siphoned. There, we learned the heartbreaking fact that people harvest bear bile only to make traditional Chinese medicine. Yet as most of the modern world would possibly agree, traditional Chinese medicine hasn't prove to have a distinct efficacy in treating diseases, rather it serves as a method to nourish and build up people's health conditions. Because of the all the above, the need for an alternative way to produce UDCA struck us as extremely urgent.

-Survey

SDSZ-iGEM-2016 Survey

1. Age

请问您的年龄是?

0-10

11-20

21-30

31-40

41-50

51-60

61-70

2. How much do you know about Bear Bile Extracting Technology?

您有多了解活熊取胆?

Nothing 没有听说过

A little bit 只是听说过, 没有深入了解

I know this but not quite 有一定的了解

I know this quite well 我对此比较了解

3. Have you ever known anyone who has or had hepatic or biliary disorders? e.g. hepatitis, fibrosis, and cirrhosis 您是否认识患有或曾患肝胆相关疾病的人? 例如: 肝炎, 肝硬化等

Yes 有

No 没有

4. If the previous answer is "yes", what's the patient's general drug treatment?

如果有, 您认识的患者一般使用的是哪类药物?

Bear bile related drugs (UDCA contained) 熊胆相关药物 (含UDCA)

Non-bear bile related drugs 非熊胆相关药物

5. If the previous answer is "Bear bile related drugs", what's the patient's preference on the type of drugs listed?

如果使用的是熊胆相关药物, 请问您认识的患者倾向于购买以下哪种?

Imported Drug 进口药

Domestic Drug 国产药

6. If you don't know anyone who has or had hepatic or biliary disorders or the person you know does not use UDCA drugs, then what's your personal preference on the type of drugs listed?

如果您不认识患有肝胆相关疾病的人或您认识的患者不使用熊胆相关药物, 请问您个人倾向于在购买药物时选择以下哪种?

Imported Drug 进口药

Domestic Drug 国产药

7. Please fill in the answers according to your personal experience/thoughts
请您按照情况填写

I chose the imported drug, because
我选择进口药，因为

I chose the domestic drug, because
我选择国产药，因为

8. Are you comfortable using/consuming products produced from genetically modified organisms? Check all categories that apply.
您愿意使用基因改造的产品吗?

Food 食物

Medication 藥物

Other 其他

Not comfortable with using any GMO products 都不愿意

9. How does the price of treatment affect your choice? To what extent will your choice be influenced by it?
治疗的价格会在什么程度上影响您的选择?

Very likely(to affect) 很大程度

Moderate level 中等程度

Not likely 很小程度

Depends (please write down your explanation to the choice)

10. Are you willing to purchase UDCA contained drug that substitutes the conventional Bear bile extracting technology?
如果有能够替代活熊取胆的药物，您是否愿意购买?

Yes 愿意

No 不愿意