

HONG KONG PHARMACEUTICAL *JOURNAL*

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Invitation letter

Hong Kong Pharmacy Conference 2014

The Annual General Meeting of the Pharmaceutical Society of Hong Kong and the 20th Anniversary of the Hong Kong Pharmaceutical Journal

A weekend trip to Taipei with the President of PSHK

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The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

An Opportunity to Turn the Tide – My Ponder After Eighteen Years of Association with HKPJ



I am very pleased to present to you the latest issue of Hong Kong Pharmaceutical Journal (HKPJ), which has a history of more than twenty years by this month. From the viewpoint of growth of a human being, it is regarded reaching a stage of mature. I believe no one would doubt that HKPJ is the only local pharmaceutical journal as there is no other similar one available in Hong

Kong. Furthermore, HKPJ has been published so regular and professional to cover some in-depth issues or studies relevant to pharmacy practices since its' birth in 1992. Except the first two volumes, I have witnessed its growth and changes in the last eighteen years; first as an author in the first two years and then became an editor for two sections and about five years ago took over the task as the editor-in-chief of this journal. Throughout these twenty years although one or a few issues were occasionally missed or delayed, all together we have published nearly 80 issues and three booklets on consolidated list of the poisons, antibiotics and dangerous drugs so far. Its existence and improvement each issue after issue is the proof of joint efforts between editors and authors. Without their devotion, hard work and contribution, its publication was quite impossible. Hence, I have to give my gratitude to all our section editors as they have been so cooperative. They have done their part so well on voluntary basis and they have tried their best to secure good articles for the section that they take care of. By comparing the numbers of qualified members to that of other healthcare professionals, pharmacy community is indeed the smallest professional body in Hong Kong. Yet we have the most colorful journal. What more important is that we frequently have a good range of articles in each issue and we should be proud of our achievement made by this small professional community.

Having said that it doesn't mean HKPJ is already good enough to meet the global standard of a professional journal. Indeed there are still plenty of room for us to improve and grow. For example, the quality of content and the originality of each article are still far below international standard and these are the areas required further enhancement. One of the major problems facing by every editor is the shortage of good article in hand. From the academic point of view, HKPJ is the flagship of the Hong Kong Pharmaceutical Society and every article present in this journal should be well written and should be present with high quality whether from educational or explorative point of view. But honestly speaking, our journal has its indigenous limitation at this moment as the number of active pharmacist in Hong Kong is small. Before it reaches to a critical mass, the recurrent of inadequate submission of articles

will always be there. Fortunately, starting from last summer we have and will continue to have more qualified pharmacists graduating from both local pharmacy schools than ever before. This means that the pharmacy community will have a steady growth in term of number from now on. This phenomenon may gradually solve the problem as more number of registered pharmacists making their endeavor. When both pharmacy schools grow and stabilized, academic staff in these two schools should also spare some efforts and manpower to keep this journal running.

Equally important is to promote the growth of this journal by increasing the number of readers. If more people read this journal, more feedback and contributions will be generated. In the past, the distribution of our journal was basically relied on mailing the hardcopy to our members, which is not only very costly but also has narrow circulation. Today, publishers of many journals, whether new or old, well known or unknown, have already switched to adopt online mode of circulation in addition to traditional mode of printing with an aim to strengthen their influences and impacts as much as possible to a larger population. Therefore, if HKPJ really wants to play an influential role in our society, we should change our mentality. Increase in number of readers is absolutely unavoidable and free accessible online is probably the only way for reaching this goal. I sincere hope that with the supports and involvements of some new bloods and also the support from both pharmacy schools, we could turn this journal to a world class one and demonstrate to the world of pharmaceutical field that we, the Hongkonger, can do it.

As I shall retire in about the next couple of years, it is really necessary to identify someone who has the same vision, sacrifice spirit and endurance to work day and night at the last minute for taking over my role as the editor-in-chief if we want this journal to be sustainable and popular. This is the opportunity for whoever wants to turn the tide.

In this issue, we are lucky to have contributions from different authors. These articles cover the whole range of different sections in our journal which has not been able to meet for some time. At the moment when you receive this issue by post, I think it will be very close to Chinese Lunar New Year of the horse. Hence, I hope that you will enjoy reading this issue at home during the spring holiday and of course, wish you a prosperous and happy New Year ahead.

Cheung Hon-yeung
Editor-in-Chief
15th January, 2014

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: editor@hkpj.org
**address: G.P.O. Box No. 3274,
General Post Office,
Hong Kong**

For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

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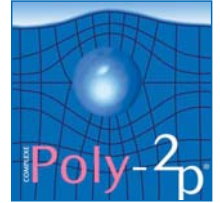
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Product of Laboratoires Dermatologiques d'Uriage, France.
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Reference

1. Bariéderm cream in the management of contact dermatitis. Toni Marius A. Ionesco, MD, PhD, Agnès GOUGEROT, MD. Saint-Louis Hospital, Paris. Saint Denis Hospital. Laboratoires Dermatologiques d'Uriage
2. Barrier cream in a series of 20 cases of chronic contact dermatitis. Prof Dominique Tennstedt, MD, PhD, Bruxelles. Dermatology Congress SIDAPA, Rome, October 2005

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Cardiovascular Outcomes for Saxagliptin Ruled Out? Not Quite Yet

Date: October 03, 2013

The cardiovascular safety and efficacy of many current antihyperglycemic agents, are unclear. In the SAVOR-TIMI 53 Trial, 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events were randomized to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95% confidence interval [CI], 0.89 to 1.12; $P=0.99$ for superiority; $P<0.001$ for noninferiority); the results were similar in the “on-treatment” analysis (hazard ratio, 1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or

heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio, 1.02; 95% CI, 0.94 to 1.11; $P=0.66$). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; $P=0.007$). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, $<0.1\%$ and 0.1% in the two groups, respectively).

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.

Source: www.nejm.org

Use of Eprex® (epoetin alfa) in Chronic Kidney Disease Patients Contraindicated? Only in Subcutaneous, as experts say

Date: October 04, 2013

The Health Sciences Authority (HSA) informed healthcare professionals that the subcutaneous (SC) administration of Eprex® is contraindicated in all chronic kidney disease (CKD) patients including end stage renal disease (ESRD) patients in Singapore. This is due to the strong association of antibody-mediated pure red cell aplasia (PRCA) with SC administration of Eprex® observed locally. The decision arose following HSA's benefit-risk assessment and its consultation with an expert panel, comprising renal physicians and haematologists, who assessed that the benefit-risk profile of Eprex® when administered subcutaneously, is no longer favourable in CKD patients in the Singapore context. Healthcare professionals are

advised that CKD patients who are currently receiving SC Eprex® should be reviewed as soon as it is possible so that they can switch to IV Eprex® or consider other therapeutic options. They are also advised to continue to closely monitor their patients for Ab-mediated PRCA when using all erythropoiesis stimulating agents (ESAs) and to remind patients on the importance and use of appropriate travel pack to maintain recommended storage temperatures during the transportation of the ESAs. HSA is working with Janssen to update the local package inserts to reflect the new contraindication.

www.drugoffice.gov.hk

Fentanyl Increases Risk of Serotonin Syndrome when Co-administrated with Serotonergic Agents

Date: October 08, 2013

The Health Sciences Authority (HSA) alerted healthcare professionals to the possibility of serotonin syndrome, a potentially life-threatening condition, when serotonergic drugs are administered concomitantly with Fentanyl, an opioid analgesic. This warning includes all fentanyl-containing products, including Durogesic® Transdermal System and Fentanyl Injection. Based on the results and conclusions of the review from Johnson & Johnson Ltd., caution is advised when these products are co-administered with drugs that affect serotonergic neurotransmitter systems. Serotonin syndrome is not an adverse drug reaction associated with the use of Durogesic® or Fentanyl Injection alone, but may occur with the concomitant use of drugs such as Selective Serotonin Re-Uptake Inhibitors (SSRIs),

Serotonin Norepinephrine Re-Uptake Inhibitors (SNRIs) and Monoamine Oxidase Inhibitors (MAOIs). If serotonin syndrome is suspected, treatment with Durogesic® or Fentanyl Injection should be discontinued.

In Hong Kong, Johnson & Johnson (Hong Kong) Ltd will issue letters to alert local healthcare professionals on the above new warnings and it has also submitted applications to change the package inserts of their products to include the above safety information. The applications are currently under evaluation and being processed.

Source: www.drugoffice.gov.hk

Australian Government Deregister Oral Ketoconazole

Date: October 10, 2013

Therapeutic Goods Administration (TGA), Australian Department of Health, is deregistering and discontinuing supply of oral ketoconazole (Nizoral) 200 mg tablets in Australia, commencing 1 December 2013.

Oral ketoconazole is an antifungal medicine that kills or stops the growth of certain types of fungi or yeasts, which cause infection. Liver injury is a known risk associated with oral ketoconazole treatment and, for this reason, a number of risk minimisation measures have been in place for a number of years.

Topical ketoconazole (Nizoral cream and shampoo) is not affected by this and will continue to be available.

TGA advised health professionals that commencing treatment

with oral ketoconazole for new patients is not recommended. If a patient is already being treated with oral ketoconazole, consider switching them to an alternative antifungal therapy. If a patient continues taking oral ketoconazole, treatment duration should be restricted to a maximum of four weeks, with a maximum daily dose of less than or equal to 400 mg. Monitoring of liver function is also strongly advised. If these tests indicate liver injury, health professionals should stop treatment immediately. Health professionals are advised to instruct patients being treated with oral ketoconazole to promptly seek medical attention if they experience signs of liver injury, such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine.

Source: Australian Department of Health

The Benefits of Combined Hormonal Contraceptives Continue to Outweigh Risks

Date: October 11, 2013

Subsequent to the previous announcement by the European Medicines Agency (EMA) in January that its Pharmacovigilance Risk Assessment Committee (PRAC) would review the newer generations combined hormonal contraceptives (CHCs) to assess whether the currently available product information provided the best information possible for patients and doctors, the EMA announced on 11 October 2013 that its PRAC concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks. The PRAC reviewed the risk of venous thromboembolism (VTE) with CHCs and confirmed that the risk of VTE with all CHCs is small and the small differences in risk among CHCs depended on the type of progestogen that they contain. Having assessed all the available data, the PRAC concluded that:

- The risk is lowest with the CHCs containing levonorgestrel, norgestimate and norethisterone: it is estimated that each year there will be between 5 and 7 cases of VTE per 10,000 women who use these medicines.
- The risk is estimated to be higher with etonogestrel and norelgestromin, with between 6 and 12 cases yearly per 10,000 women.
- The risk is also estimated to be higher with gestodene,

desogestrel, drospirenone, with between 9 and 12 cases yearly per 10,000 women.

- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs, but further studies are ongoing or planned.
- For comparison, in women who are not using CHCs and who are not pregnant, there will be around 2 cases of VTE each year per 10,000 women.

The review also looked at the risk of arterial thromboembolism. This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen. When prescribing a CHC, healthcare professionals are advised to assess a woman's individual risk for blood clots regularly, as the risk changes over time. Risk factors include smoking, being overweight, increasing age, having migraines, family history of VTE and having given birth in the previous few weeks. The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom (UK) followed EMA's recommendation, and advised that patients on these medicines should continue to take their contraceptive pills.

Source: www.drugoffice.gov.hk

Australian Warns Safety Concern for Mefloquine Hydrochloride (Lariam)

Date: October 11, 2013

The Therapeutic Goods Administration (TGA), Australian Department of Health, announced that the safety information for the anti-malaria drug mefloquine hydrochloride (Lariam) have recently been updated to include new information about the potential for visual disturbances.

The new information was added following a review by the sponsor which included a cumulative review of available evidence from the company's non-clinical studies, the global drug safety database, the UK General Practice Research Database and the published literature.

To summarise the new information regarding visual disturbances:
1. Treatment with Lariam may be associated with an increased risk

of eye disorders including cataract, retinal disorders and damage to the optic nerve. These may occur during treatment or for several weeks afterwards.

2. Symptoms of these eye disorders include visual impairment and blurred vision.
3. In some cases the patient recovered very slowly but there have also been reports of permanent after-effects.
4. Lariam treatment may need to be stopped if there are signs of certain conditions (such as retinal disorders or optic nerve damage).

Source: <http://www.tga.gov.au/safety/alerts-medicine-mefloquine-hydrochloride-131011.htm>

Cinacalcet May Cause Arrhythmia, Warns the Canadian Government

Date: October 15, 2013

Health Canada reviewed the safety of the drug Sensipar (cinacalcet) that identified a possible link between the drug and abnormal heart rhythm associated with low blood calcium. New warnings have been added to the labelling information advising of this risk.

Cinacalcet is used for treating disorders of the parathyroid gland that result in abnormal blood calcium levels. It is well known to cause lower-than-normal levels of blood calcium (hypocalcemia). Low blood calcium can cause electrical changes in the heart known as "QT prolongation" and arrhythmia, which can be serious and, in some cases, may lead to sudden death.

It is yet to determine what role cinacalcet may have played in the development of QT prolongation or arrhythmia, as other risk factors were present at the same time. However, given the effect

of low blood calcium on the heart, the possibility of developing QT prolongation or arrhythmia could not be ruled out.

Health professionals are advised to monitor patients for signs of low blood calcium, and prescribe cinacalcet with caution in patients with other risk factors for QT prolongation, such as known congenital long QT syndrome (an inherited heart condition), or in patients who are taking other drugs known to cause QT prolongation. For patients treated with cinacalcet for chronic kidney disease and receiving dialysis, reduce dose or stop use if low blood calcium, signs of QT prolongation, or arrhythmia continue. For these patients, cinacalcet should be contraindicated if hypocalcemia develops.

Source: <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/./36267a-eng.php>

A Randomized Trial of Colchicine for Acute Pericarditis

Date: October 17, 2013

Colchicine has been found to be effective for the treatment of recurrent pericarditis by its anti-inflammatory nature. However, there is no conclusive data showing the benefit in the use of colchicine during a first attack of acute pericarditis and in the prevention of recurrent symptoms.

A randomized, double-blind trial, 240 patients with acute pericarditis were assigned to receive either colchicine (0.5 mg twice daily for 3 months for patients of body weight >70 kg or 0.5 mg daily when body weight ≤70 kg) or placebo in addition to conventional anti-inflammatory therapy with aspirin or ibuprofen. The primary study outcome was incessant or recurrent pericarditis.

The primary outcome occurred in 20 patients (16.7%) in the colchicine group and 45 patients (37.5%) in the placebo group (RR

reduction in the colchicine group, 0.56; 95% CI, 0.30 to 0.72; NNT, 4; P<0.001). Colchicine reduced the rate of symptom persistence at 72 hours (19.2% vs. 40.0%, P=0.001), the number of recurrences per patient (0.21 vs. 0.52, P=0.001), and the hospitalization rate (5.0% vs. 14.2%, P=0.02). Colchicine also improved the remission rate at 1 week (85.0% vs. 58.3%, P<0.001). Overall adverse effects and rates of study-drug discontinuation were similar in the two study groups. No serious adverse events were observed.

From the study results, it seems that colchicine, when added to conventional anti-inflammatory therapy for the management of acute pericarditis, significantly reduced the rate of incessant or recurrent pericarditis.

Source: www.nejm.com

The New Oral Anticoagulants: Post-marketing Increased Risk of Bleeding

Date: October, 2013

MHRA issued letter for healthcare professionals regarding the risk factors for bleeding of the new oral anticoagulants. Clinical trials and post-marketing experience have shown that major bleeding events, including events leading to death, are not confined to vitamin K antagonists/LMWH but are also significant risks for the new oral anticoagulants. Furthermore, post-marketing reports indicate that not all prescribers are sufficiently aware of the product information in terms of managing bleeding risks.

Healthcare providers should consider the individual patient risk of bleeding and observe posology, contraindications, and warnings and precautions for use. While differences in contraindications exist between the new oral anticoagulants, they share the following contraindications:

- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for

major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, other) except under the circumstances of switching therapy to or from the medicine, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

Source: <http://www.mhra.gov.uk/index.htm#page=DynamicListMedicines>

FDA Warns Potiga (Ezogabine) May Link To Retinal Abnormalities And Blue Skin Discoloration

Date: November 1, 2013

FDA approved changes to the drug label of the anti-epileptic medication Potiga (Ezogabine), which may pose risks of abnormalities to the retina in the eye, potential vision loss, and skin discoloration, all of which may become permanent. The revised label includes a new boxed warning, because of the risk of abnormalities to the retina. FDA advises that Potiga use

be limited to patients who have not responded adequately to several alternative therapies to decrease the frequency of seizures, or epilepsy, and for whom the benefits of treatment outweigh the risks.

Source: <http://www.fda.gov/Safety/MedWatch/./ucm349847.htm>

Second Thought When Switching Anti-epileptic: MHRA Issues New Update

Date: November 13, 2013

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has issued new guidance to healthcare professionals and patients regarding anti-epileptic drugs (AEDs) prescribing. This is released after a review done by the Commission on Human Medicines (CHM) which evaluated the evidence on patients switching between different manufacturers' products of particular AEDs. The conclusion was whilst there was no clear evidence of harm associated with switching products, an effect in some patients, for some drugs, could not be completely ruled out.

The potential effects of switching may compromise seizure control or the occurrence of side effects, or both. These risks can be associated with switching between a proprietary and a generic product, and between different generic products.

CHM advised that AEDs could be classified into three categories. These categories aim to help prescribers and patients decide whether it was necessary to maintain continuity of supply of a specific manufacturer's product.

Category 1: For these drugs doctors are advised to ensure that their patient is maintained on a specific manufacturer's product. The

AEDs in this category are: phenytoin, carbamazepine, phenobarbital, primidone.

Category 2: For these drugs the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer taking into account factors such as seizure frequency and treatment history. The AEDs in this category are: valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate.

Category 3: For these drugs it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors. The AEDs in this category are: levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin.

If patients have any concerns about, or problems with, their antiepileptic medicine, they should speak to a healthcare professional such as a doctor, pharmacist, or nurse.

Source: <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON335050>

Going Nuts?

Date: November 23, 2013

It has been speculated that increased nut consumption has been associated with a reduced risk of major chronic diseases, including cardiovascular disease and type 2 diabetes mellitus. However, the association between nut consumption and mortality remains unclear.

Researchers studied the association between nut consumption and subsequent total and cause-specific mortality among 76,464 women in the Nurses' Health Study (carried out between year 1980–2010) and 42,498 men in the Health Professionals Follow-up Study (carried out between year 1986–2010). Participants with a history of cancer, heart disease, or stroke were excluded. Nut consumption was assessed at baseline and updated every 2 to 4 years.

In the 3,038,853 person-years of follow-up, 16,200 women and 11,229 men died. Nut consumption was inversely associated

with total mortality among both women and men, after adjustment for other known or suspected risk factors. The pooled multivariate hazard ratios for death among participants who ate nuts, as compared with those who did not, were 0.93 (95% confidence interval [CI], 0.90 to 0.96) for the consumption of nuts less than once per week, 0.89 (95% CI, 0.86 to 0.93) for once per week, 0.87 (95% CI, 0.83 to 0.90) for two to four times per week, 0.85 (95% CI, 0.79 to 0.91) for five or six times per week, and 0.80 (95% CI, 0.73 to 0.86) for seven or more times per week ($P < 0.001$ for trend). Interestingly, there had been significant inverse associations found between nut consumption and deaths due to cancer, heart disease, and respiratory disease.

So, nuts maybe good for you, afterall!

Source: www.nejm.com

The “Come Back” of Rosiglitazone

Date: November 25, 2013

FDA has determined that recent data for rosiglitazone-containing drugs do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea. As a result, FDA is requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on FDA review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI).

Previous data from a large, combined analysis of mostly short-term, randomized clinical trials of rosiglitazone had suggested an

elevated risk of heart attack, so FDA required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program. The program restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks.

Although some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines still remains, in light of the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, FDA's concern is substantially reduced and the rosiglitazone REMS program requirements will be modified.

Source: <http://www.fda.gov/Safety/MedWatch/./ucm376683.htm>

New Labelling Requirement of Proprietary Chinese Medicines containing Polygoni Multiflori Radix (何首烏)

Date: December 31, 2013

On 31 December 2013, the Chinese Medicine Division of the Hong Kong Department of Health issued a letter to all registration holders of proprietary Chinese medicines (pCm) containing the ingredient Polygoni Multiflori Radix (何首烏) that they are required to fulfil the labelling and package inserts requirements by 30 June 2014. The pCm must show the ingredient Polygoni Multiflori Radix in the labelling and add the ingredient name and quantity in the package insert of the pCm. Moreover, they are required to add in the package inserts of the pCm, under its contraindications:

1. Not to be used by people with liver and renal insufficiency.
2. Not to be used by pregnant women.
3. Not recommended to be used by people with the history of damaged liver by the ingredient or other drug formulation containing the ingredient.

And in the package inserts, under the precautions to be taken regarding its use:

1. During usage of the pCm, it is recommended to monitor the liver function indicators, and if the liver function indicators are abnormal or

the patients develop exhaustion, loss of appetite, dislike oil, nausea, yellowish urine, jaundice in the eyes and skin and clinical symptoms representing damage of liver function or worsening of liver function indicators and aggravation of damaged liver symptoms, the pCm should be stopped immediately and consult the physician.

2. Strictly follow the dosage direction, and not to exceed recommended dosage nor continuous prolonged use of the pCm.
3. Elderly patients and patients with liver damage history are to use the drug with caution.
4. Nursing mothers should stop the usage of the drug or stop nursing the baby.
5. No safety data is available on the usage of the drug in children. It is advised to use the drug in children with caution.
6. People with the family history of damaged liver by the ingredient or other drug formulation containing the ingredient should use the drug with caution.
7. To avoid use of this pCm together with other drugs with liver toxic effects .

Source: Chinese Medicine Division of the Department of Health

Consultancy Services – A New and Little-Known Role of a Pharmacist

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Background

As both an entrepreneur and a pharmacist, Mr. Peter Leung (Figure 1) has great passion for providing consultancy services to foreign companies related to health science. He also put attention on the development of young pharmacists and the pharmacy profession.



Figure 1. A portrait of Mr. Peter Leung

Peter Leung owns a consultancy firm and is the current vice-president of the Pharmaceutical Society of Hong Kong. He has a lot of experience in his pocket and has faced many challenges before arriving at his various achievements.

Mr. Leung obtained his Bachelor of Pharmacy in the University of Queensland in Australia in 1993. He became a registered pharmacist after 1 year of internship in the retail sector and a written examination. After that, he went on to work in a hospital and decided to pursue his study in accounting at the same time. After half a year, he made a U-turn and decided to relocate back to Hong Kong as he felt that is where his home and family. He worked as a dispenser while he sat for the registration examination in Hong Kong and was successfully registered in 1996. His internship in the hospital sector made him feel that hospital work is too much a routine for him. He then decided to work in the community sector due to his outgoing personality. During which, he had the opportunity to have met many fellow colleagues from other sectors and got to know their job natures. He left the community sector after a considerable period of time as he felt he needed some new challenges and chance to learn more new things. The opportunity arose when one of the many people he met during his time in the community successfully persuaded him to join a drug distribution company. He worked at different positions from 2005 to 2009, before leaving the company and establishing his own consultancy firm and worked for it till the present.

What was your job and working experience in a drug distribution company?

"I worked as the quality assurance manager for the company and my job was to pursue quality management. I had many duties, such as managing dangerous drugs distribution, drug import and export and secondary packaging. The company, despite of having to comply with both ISO (International Organization for Standardization) and internal standards, the system of secondary packaging was still not ideal," Mr. Leung explained. After identifying the problems, he upgraded the system by setting standard operating procedures and training programs for his colleagues. During his time with the company, he had gained a lot of experience in making contact with other multi-national drug companies and made learned to improve the system according to the feedbacks he received from various company audits.

During 2008 to 2009, he worked as a logistic manager and was responsible for managing the warehouse and the company delivery service. Facing challenges such as space constraints, he still managed to improve the system and the staff training program.

Why would you establish a consultancy firm and what is the scope of business of the company?

"The implementation of Good Manufacturing Practice in 2009 has greatly increased the workload of local drug manufacturers. Therefore, I established a consultancy company to help my wife out, who works as a pharmacist in a local drug manufacturing company," he said. "My company mainly provides consultation services to health products or food companies and foreign pharmaceutical companies. Usually, we provide item reviews and provide consultation on matters related to regulatory affairs. My company also gives consultation in other areas such as sales and marketing," he further explained.

It can be imagined that Mr. Leung have faced many difficulties and obstacles along the way, but he said that his past working experience had helped him to resolve them one by one. He found a good example in learning how to communicate effectively with customers and understanding their needs during his times working in customer service.

You have worked in many different sectors, which sector did you enjoy the most and what experience could you share with readers?

"I enjoyed working in all sectors because I keep learning new things from different jobs. When working in retail pharmacy, I learned to run a business with the consideration of rent and staff training. I also gain knowledge in new products that has just been launched and had great satisfaction counseling customers. In the drug distribution company, I have widened my horizons as I took responsibilities that are very different from the past, such as handling the import and export of dangerous drugs and psychotropic substances. By participating in audits and regional meetings, I learned a lot on how the system of quality assurance can be improved and different styles of running a business. By working in my consultancy firm, I learned more about customer needs and requirements," said Mr. Leung.

When talking about memorable experiences in his jobs, his answer was numerous. He solved many health problems of customers and helped them to manage their health in the retail pharmacy setting. In the drug distribution company, one of the most unforgettable experiences is the establishment of the Good Storage and Distribution Practice as he had overcome many challenges along the way, such as budgeting and hardware. Helping foreign companies to understand Hong Kong market and law requirements in the consultancy firm were also memorable as this could help them seek opportunities for development in Hong Kong.

What is the future plan of you and your company?

"I want to continue to provide information to foreign companies to save their time and capital when they want to develop their business in Hong Kong. Moreover, I might like to seek more pharmacists to help me running this consultancy firm in the future," said Mr. Leung.

What suggestions can you give to new pharmacy graduates?

"I think that new graduates should know how to respect others because everyone bounds to have something that they could learn from and they should ask more questions to improve their skills and knowledge. Young graduates should learn not to count their loss from inputting to the profession such as working as a volunteer or joining society activities. It is because by doing these, it can help the development of the profession as well as themselves. New graduates are at the prime time to do such things as they are young and have fewer burdens from

family and children," Mr. Leung suggested. To encourage the graduates, Mr. Leung used himself as an example. Apart from working for the Pharmaceutical Society of Hong Kong for more than ten years, he is also helping to review the drug dispensing system and providing staff training to a non-government organization which serves the mentally retarded patients. Lastly, Mr. Leung encouraged graduates to "work hard, learn more, and focus on broad and long-ranged targets".

Learning from the interview

Mr. Leung has worked in different sectors and these experiences are important to his current success. His story tells us that changes at suitable moments may hold the key to better future development. We should embrace changes and learn to greet the upcoming challenges with a brave face.

From the interview, it was obvious that Mr. Leung is passionate about the pharmacy profession and his jobs. However, keeping that passion alive is easily said than done. Keeping an open-mind and dedication to life-long learning may be a way to preserve that determination for continuous improvements and contributions to a profession.

Author's background

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An Overview of Contemporary Treatment for Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a progressive, destructive and lifelong health problem, with substantial clinical consequences. Without proper medical treatment, RA will eventually lead to irreversible joint damage and deformity in patients. Various medications, such as disease-modifying anti-rheumatic drugs (DMARDs) or biologics, are available on the market to treat RA. However, these medications have their own drawbacks. Newer types of medication such as the use of new compounds targeting intracellular pathways to treat RA have been developed. The US FDA recently approved one of these DMARDs. With increasing concerns about patient-care, pharmacists are expected to play a more important role in the treatment of RA. Hence, pharmacists should be better equipped to offer patient counselling, encourage patient compliance, and management of RA and its effects when dispensing an anti-rheumatic drug.

Keywords: Rheumatoid arthritis; Disease-modifying anti-rheumatic drugs (DMARDs); Biologics

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, autoimmune, inflammatory disease that affects mainly the joints throughout our body. Symptoms are characterized by joint pain, swelling and stiffness which will eventually lead to a rapid loss of function, joint destruction, permanent deformity and reduced life expectancy.⁽¹⁾

The prevalence rate of RA is approximately 0.5 to 1% of the adult population in the developed world.⁽²⁾ In Hong Kong, around 0.7% of the population was diagnosed with RA.⁽³⁾ Although the exact etiology of RA is unknown, it is believed that RA is related to genetic susceptibility, infection, and other environmental factors. The inflammation typically begins in the synovial lining of the joint with proliferation of the synovial cells and infiltration of the inflammatory cells. In the early stages of RA, the synovial membrane begins to invade the cartilage. In time, the synovial membrane will transform into inflammatory tissue (formation of pannus), the tissue will then invade and destroy adjacent cartilage and bone, which will eventually lead to irreversible joint damage and deformity.⁽⁴⁾

CLASSIFICATION OF RHEUMATOID ARTHRITIS

Currently, the classification of RA is based on a joint American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria.⁽⁶⁾ The targeted population has to meet requisite criteria of at least one joint with definite clinical synovitis or with synovitis that cannot be better explained by another disease. After meeting the criteria, the subject will then be scored in four areas:

- A) The number of joints involved
- B) Serology testing (rheumatoid factor and/or anti-citrullinated protein antibodies)
- C) Testing of acute-phase reactants (C reactive protein and/or the erythrocyte sedimentation rate)
- D) Duration of symptoms.

A total score equal to or greater than six is required for classification of RA. Under these criteria, it is possible for a patient to be classified with RA without serology or acute phase reactant testing.

ASSESSMENT OF RHEUMATOID ARTHRITIS

Apart from the RA classification, several scoring systems are available to assess disease progression or improvement of the condition. These can be grouped into "Clinical" and "Radiographic" scoring systems.

The common "clinical" scoring system includes the ACR definition of response criteria (ACR20, ACR50, ACR70); Disease Activity Score (DAS) or Disease Activity Score 28 (DAS28); EULAR criteria of response; and Health Assessment Questionnaire (HAQ). The common "Radiographic" scoring system includes the modified total sharp score (mTSS).

ACR Response Criteria (ACR20, ACR50, ACR70)

The ACR scores are usually presented as ACR20, ACR50 and ACR70. The definition of ACR20 indicates a 20% improvement in the tender and swollen joint counts and 20% improvement in three of the following five parameters: the patient's global assessment, the physician's global assessment, the patient's assessment of pain, the degree of disability and the level of acute-phase reactant such as C-reactive protein.⁽⁵⁾

Similarly, the definition of ACR50 is a 50% improvement in the above criteria and ACR70 means 70% improvement in the above criteria. For example, if a study reports that 55% of patients achieved ACR20, that means 55% patients in that study achieved a 20% improvement in tender or swollen joint counts and 20% improvement in three of the five criteria.

Disease Activity Score (DAS) or Disease Activity Score 28 (DAS28)

DAS is a statistic mathematic calculation developed by EULAR to quantify a single composite score.⁽⁶⁾ The calculation is based on several parameters including the RAI (Ritchie Articular Index: a joint count that grades the tenderness of the joint), the number of swollen joints, the erythrocyte sedimentation rate (ESR) and assessment of the patient's general health. DAS28 is different from DAS only in the total number of joint counts in the calculation. DAS28 measures 28 joints while DAS measures 44 joints.⁽⁷⁾ After the score is calculated, the level of disease activity affecting the patient can be determined, for example, DAS <1.6 or DAS 28 <2.6 is defined as remission.⁽⁸⁾

EULAR criteria of response

This is determined as the change in DAS or DAS28 with reference to the baseline value. A drop in DAS or DAS28 is classified as good response, moderate response and no response. For example, improvement in DAS or DAS18 from the baseline ≤ 1.2 is defined as good response, >0.6 and ≤ 1.2 as moderate response, and ≤ 0.6 as no response.⁽⁹⁾

Health Assessment Questionnaire (HAQ)

The HAQ comprehensively measures patient-oriented outcomes in five dimensions; disability, discomfort, drug side effects (toxicity), dollar costs and death (such as mortality-related data).⁽¹⁰⁾ Patients will be asked to score questions that are related to these dimensions. The overall average score represents the patient's health status.

Modified Total Sharp Score (mTSS)

The mTSS is a score that looks into a number of joints in the wrist, hand and forefoot. The score is measured by the degree of joint erosions and the degree of joint space narrowing. The severity of the radiological progression will merit a higher score.⁽¹¹⁾ Generally, the mTSS is measured regularly and compared to the baseline score to determine whether the disease has progressed or improved. A positive score indicates the disease has progressed while a negative score means the disease has improved.

Remission

The ultimate goal of RA treatment is the induction and maintenance of clinical remission. The ACR defines remission as: morning stiffness (≤ 15 mins), no fatigue, no joint pain, no joint tenderness, no joint swelling and ESR (< 30 mm/h for a female or 20 mm/h for a male).⁽¹²⁾ Additionally, DAS/DAS28 defines remission as achieving a score of <1.6 (DAS) and <2.6 (DAS28) respectively.

CURRENT MEDICAL TREATMENT

Early intervention with DMARDs is now known to be crucial to limit the progression of structural damage in RA diseases.⁽¹³⁾ Drug therapy for RA consists of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), which are used primarily to relieve pain; disease-modifying anti-rheumatic drugs (DMARDs), which prevent joint destruction; and corticosteroids, which have an anti-inflammatory effect.

Simple analgesics such as acetaminophen, tramadol, and dihydrocodeine have no anti-inflammatory properties but are useful for controlling pain and soreness associated with RA.⁽¹⁴⁾ NSAIDs are slightly stronger than acetaminophen due to their anti-inflammatory properties. Although NSAIDs are very similar, individuals have varied responses to different NSAIDs and hence the choice of NSAID differs between patients.⁽¹⁷⁾ The dose of the chosen NSAID should be increased gradually over 1 or 2 weeks to reduce the risk and severity of side effects. Newer generations of NSAIDs, Cyclooxygenase-2 (COX-2) inhibitors such as celecoxib, are useful in patients at an increased risk of gastrointestinal (GI) symptoms.⁽¹⁷⁾ The use of corticosteroids is controversial due to the associated adverse effects. Where required, the dose should be kept as low as possible to reduce the risk of adverse effects such as osteoporosis, hypertension, cataracts, infections, and skin fragility.⁽¹⁵⁾ Long-term, low-dose glucocorticoid therapy is justifiable, especially if the bones are protected for osteopenia, whereas higher doses are normally used as a bridge between treatments and until DMARDs become effective.^(18,19)

While NSAIDs provide symptomatic relief, they do not halt disease progression. DMARDs, on the other hand, have the effect of slowing down the disease,⁽²⁰⁾ even though they take slightly longer to work than NSAIDs and analgesics. Thus, DMARDs interfere with the disease process.⁽¹⁶⁾ There is evidence that DMARD therapy is most effective when initiated early on in the disease, since irreversible joint damage occurs in the first 2 years.⁽¹⁹⁾ In fact, a recent study comparing DMARDs, glucocorticoids, biologics, and combination treatments concluded that DMARDs should be retained as first-line therapy.⁽¹⁷⁾ However, since the effects of DMARDs are not immediate, they should be taken for at least 6 months.^(21, 22) If no benefit is evident during this time period, a second DMARD may be tried. In some cases, combining DMARDs may offer effective therapy.⁽²²⁾

First choices for DMARDs include hydroxychloroquine (HCQ) and sulfasalazine (SSZ) or methotrexate (MTX) for patients with highly active disease.⁽¹⁸⁾ Traditional DMARDs such as MTX are used as standard/ first-line therapy, either alone or in combination in the majority of RA cases⁽²²⁾ due to its favorable efficacy, toxicity profile, and low cost.^(19,20,21) If the response is inadequate, an additional DMARD or a biologic agent is added to the initial treatment until disease control is achieved.

As the benefits of early aggressive intervention in RA patients become increasingly evident, the therapeutic paradigm continues to evolve. Some rheumatologists now start with a higher DMARD dose and escalate dosage more rapidly to achieve a response.⁽¹⁹⁾ Biologic agents are also being used

earlier in the treatment continuum and sometimes used as first-line therapy.⁽¹⁹⁾ For non-responders, combination therapy may be the next step. In patients with well-controlled disease, however, the goal is to reduce or discontinue concomitant medications and treat with a single agent whenever possible to reduce the potential for toxicity.^(17,18,20)

BIOLOGICS OVERVIEW

Biologics is a term used to describe products produced through biological processes rather than by traditional chemical technology. According to the US FDA, a biologic is defined as a medicinal product, 'the active substance(s) of which is (are) produced from or extracted from a biological (living) system, by using recombinant DNA technology- a process of combining existing elements of DNA, proteins, cells or organisms in a laboratory to create a new substance. It can be made up of living cells or tissues or complex protein structures and can be sourced from microorganisms (such as bacteria) and animal or human tissues.⁽²¹⁾ Substantial research has been conducted over the past 30 years to further our understanding of biologics in the treatment of inflammatory conditions. Biologics are frequently emerging in today's market. **Table 1** shows the biologic therapies currently available on the HK market. It is not difficult to conclude that these products are all belongs to the monoclonal antibodies against TNF or blocker of a receptor on T-cell and they are administered via parenteral route.

Table 1. Existing biologic therapies available on the HK market. (Listed in chronological order by brand name)				
Medication	Chemical Names	Company	Mechanism of Action	Route of Administration
Actemra	Tocilizumab	Roche	Anti-IL-6 receptor mAb, humanised	IV infusion
Enbrel	Etanercept	Pfizer	Soluble TNF α receptor fusion protein, fully human	SC
Humira	Adalimumab	Abbott	TNF α mAb, human	SC
Orencia	Abatacept	Bristol-Myers Squibb	Co-stimulation T-cell modulator, fusion protein, CTLA4	IV infusion
Remicade	Infliximab	Janssen	TNF α chimeric mAb	IV infusion
Simponi	Golimumab	Janssen	TNF α fully human mAb	SC

*SC-subcutaneous injection, IV-intravenous

Types of biologics available on the market

1. Anti-TNF

TNF is a potent pro-inflammatory cytokine, which exerts diverse effects on a variety of cells and plays a critical role in the pathogenesis of chronic inflammatory diseases. TNF is produced mainly by monocytes, macrophages, B cells, T cells and fibroblasts.⁽²²⁾ It is generated in a precursor form called transmembrane TNF, which is expressed on the surface of the cell after synthesis. It is subsequently released as soluble TNF (sTNF) through the cleavage of the membrane-anchoring domain by TNF.⁽²³⁾ Binding of TNF to its receptors triggers the recruitment of intracellular adaptor proteins, which leads to activation of a complex intracellular signaling process. Anti-TNFs are used as first line therapy after DMARDs in several international guidelines. Infliximab, Adalimumab, Golimumab and Etanercept belong to the Anti-TNF group. Infliximab (Remicade) is a chimeric monoclonal anti-TNF antibody; which neutralises the biological activity of TNF- α and inhibits binding of TNF- α with its receptors.⁽²⁴⁾ Adalimumab (Humira)

and Simponi (Golimumab) are both human monoclonal anti-TNF antibodies that bind specifically to TNF-alpha and blocks its interaction with p55 and p75 cell surface TNF receptors.^(25,26) Etanercept (Enbrel) has a different structure in the anti-TNF class. Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind TNF molecules. Etanercept inhibits binding of TNF- α and TNF- β to cell surface TNFRs, rendering TNF biologically inactive.⁽²⁷⁾ All four anti-TNF agents are licensed for RA, Ankylosing Spondylitis (AS), Psoriasis (PsO), Psoriasis Arthritis (PsA), and Juvenile Idiopathic Arthritis (JIA).

2. Anti Interleukin 6 (IL-6)

Interleukin 6, (IL-6) is a pleiotropic inflammatory cytokine produced by T cells, monocytes, macrophages, and synovial fibroblasts. IL-6 is involved in diverse biologic processes, such as the activation of T cells, the induction of acute-phase response, stimulation of the growth and differentiation of hematopoietic precursor cells, and the proliferation of synovial fibroblasts.⁽²⁸⁾ Tocilizumab (Actemra) is a recombinant, humanised, anti-human interleukin 6-receptor (IL-6R) monoclonal antibody of the immunoglobulin IgG1 subclass. It binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and IL-6R), and has been shown to inhibit IL-6 mediated signaling through these receptors. Indications include treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies in combination with MTX, and treatment of systemic juvenile idiopathic arthritis (sJIA) in patients ≥ 2 yrs, who responded inadequately to previous therapy with NSAIDs & systemic corticosteroids. Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued MTX treatment is inappropriate.⁽²⁹⁾

3. Anti-CD20

CD20, or B-lymphocyte antigen CD20, is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells beginning at the pro-B phase (CD45R+, CD117+) and progressively increasing in concentration until maturity.⁽³⁰⁾ In humans, CD20 is encoded by the MS4A1 gene.⁽³¹⁾ MabThera (Rituximab) is a chimeric mAb that binds to the CD20 protein present on the surface of most normal and malignant B-cells, causing lysis of these cells. It is indicated as 2nd line biologics (after anti-TNF failure) for the treatment of RA in several international guidelines.⁽³²⁾

4. Anti-T cell

T cells, or T lymphocytes, belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity. They are distinguished from other lymphocytes, such as B cells and natural killer cells (NK cells) by the presence of a T cell receptor (TCR) on the cell surface. They are called T cells because they mature in the thymus. There are 5 main types of T cells, each with a distinct function.

Orencia (Abatacept) is a biologic, which targets T cells and prevents their full activation. It is a soluble recombinant fusion protein selective T cell co-stimulation modulator (CTLA4Ig) that competitively binds CD80/CD86 on human APCs.⁽³³⁾ Ordinarily, full T cell activation requires 1) binding of the T cell receptor to the antigen-MHC complex on the APC, and 2) a co-stimulatory signal provided by the binding of CD28, a T cell protein, to the B7 protein on the APC. Abatacept, which contains a high-affinity binding site for B7 works by binding to the B7 protein on APCs and prevents them from delivering the co-stimulatory

signal to T cells, blocking their activation. Orencia is licensed for indications that include moderate to severe active RA in adults and may be used as monotherapy or concomitantly with DMARDs but not as a TNF antagonist. It is also indicated for moderate to severe active polyarticular JIA in paediatric patients > 6 years of age, and may be used as monotherapy or concomitantly with MTX.⁽³⁴⁾

COMMON SIDE EFFECTS OF BIOLOGICS

All classes of biologics carry a safety warning of increased risk of opportunistic infections (OIs), including tuberculosis (TB), hepatitis, bacterial sepsis, invasive fungal infections and infections due to other opportunistic pathogens. Skin reactions to injection also occur in less than 30% of biologic treated patients, and such patients usually complain of localised rash, burning, or itching at the site of injection.

A TB skin test is usually performed prior to starting biologics, especially Anti-TNF. Treatment with these agents should be stopped if patient has an active infection, is on antibiotics or has a high fever.

POTENTIAL NEW MEDICATIONS BASED ON OTHER PATHWAYS

In recent years, multiple companies have become involved in efforts to develop orally active small molecules that specifically target disease-associated molecules and signaling pathways, which are mediated by cytokine receptors. Scientists have attempted to target cytokines and their receptors in order to treat immunological diseases. Different signaling pathways have been identified such as the mitogen-activated protein kinase (MAPK) pathway, spleen tyrosine kinase (Syk) signaling pathway, Bruton's tyrosine kinase (BTK) family of non-receptor tyrosine kinases, the PI3K pathway, the cyclic adenosine monophosphate-protein kinase A (cAMP-PKA) pathway, protein kinase C (PKC) pathway, the nuclear factor k light-chain-enhancer of activated B cells (NF-κB) pathway, and the Janus kinase (JAK) pathway. **Figure 1** below shows the mechanisms for different intracellular signaling pathways.^(35,36,37,38,39)

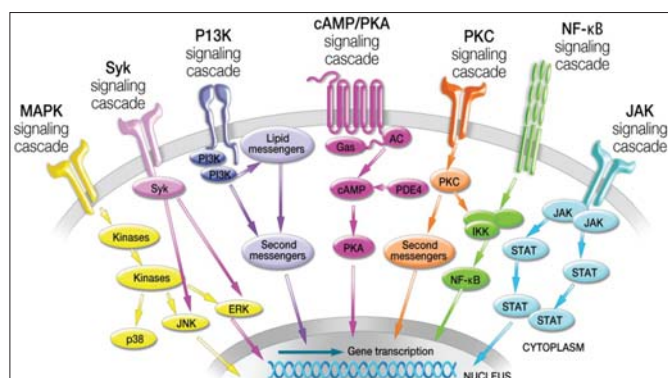


Figure 1: Different Cytokine Signal Pathways^(35,37)

Of all the signaling pathways, the Janus kinase (JAK) pathways are among those that are utilised by multiple cytokines. The binding of certain cytokines to their receptors on a cell membrane activates intracellular JAK proteins. JAKs activate intracellular proteins called signal transducers and activators of transcription (STAT). Activated STATs dimerise and move to the cell nucleus. Once in the nucleus, STATs

function as transcription factors to activate gene transcription. JAK signaling stimulates the production of pro-inflammatory proteins (e.g. cytokinease and chemokines) which in turn contribute to the persistent inflammation and joint destruction found in RA. JAK 3 is a subtype of JAK. Mutation of the JAK3 gene would result in Severe Combined Immune-Deficiency (SCID) in which T cells and natural killer (NK) cells are absent. This indicates that JAK3's antagonising action could have immunosuppressive effects.⁽⁴⁰⁾

Tofacitinib (CP 690,550)

Tofacitinib (CP-690, 550) is a selective oral inhibitor of the Janus kinase (JAK) family of kinases, including JAK1 and JAK3, a tyrosine kinase that mediates signal-transduction activity.⁽⁴¹⁾ Recently, the US FDA approved the use of XELJANZ (Tofacitinib) for the treatment of adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Tofacitinib is the first RA treatment in a class of medications known as JAK inhibitors. It is a novel oral Janus kinase inhibitor that inhibits the binding of cytokine to its specific cell-surface receptor causing the receptor chains to polymerise and activate the associated JAKs. Tofacitinib binds the catalytic cleft in the kinase domain of JAKs, modulating the JAK signaling pathways at the point of JAK phosphorylation, preventing activation of JAK and thus the signal transducer and activators of transcription (STAT).^(41,42,43) Apart from the treatment of rheumatic diseases, researchers are also exploring the use of tofacitinib in other therapeutic areas such as dermatology,⁽⁴⁴⁾ and gastroenterology.⁽⁴⁵⁾ Some Phase 2 study results look promising and it might be possible to expand the indications for Tofacitinib in future.

PHARMACISTS' ROLE IN RA MANAGEMENT

A complete rheumatoid arthritis management team should consist of rheumatologists, occupational therapists and nurses.⁽⁴⁶⁾ In addition, pharmacists also play a key role in RA management. Pharmacists are important in assisting patients on RA medications to optimize their overall health outcomes.⁽⁴⁷⁾ Through pharmacist counselling, patients will learn how to use RA medications correctly and understand the expected outcomes.⁽⁴⁸⁾ Another important point is that pharmacists are experts in assessing for potential drug interactions and are able to stress the importance of drug compliance.^(49,50,51) Furthermore, pharmacists should be easily accessible to address patient concerns regarding their current RA therapy and any adverse drug reactions.

CONCLUSION

Rheumatoid arthritis is a common chronic disease affecting all age groups. Over the last decade, simple analgesics such as NSAIDs and DMARDs have been standard therapy for RA treatment. Methotrexate, one of the first lines of DMARD, is regarded as the gold standard therapy for patients with moderate to severe RA. Recent advance in biotechnology has seen the development of biologics and some intracellular small molecules for the treatment of RA. With an increasingly important role in patient compliance and the management of side effects, pharmacists must become familiar with the latest advances in RA treatment and technology.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pcccchk.com) to fill in their answers there.)

1. Which of the following is not a common sign and symptom of Rheumatoid Arthritis (RA)?

- a. Synovitis
- b. Joint stiffness
- c. Joint pain
- d. Back Pain

2. Which of the following risk factor does not contribute to the potential development of Rheumatoid Arthritis (RA)?

- a. Genetic factor
- b. Enviromental factor
- c. Male
- d. Infection

3. Which are the joint American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria for Rheumatoid Arthritis (RA)?

- 1. Joint involvement
- 2. Serology
- 3. Acute-phase reactant
- 4. Duration of symptoms

- a. 3,4
- b. 2,3,4
- c. 1,2,3,4
- d. 2,4

4. DAS28 measures 28 joints. How many joints do DAS measures?

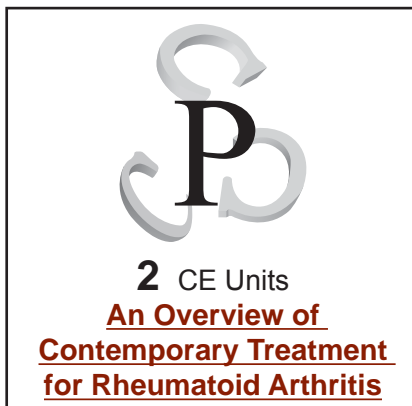
- a. 38
- b. 41
- c. 42
- d. 44

5. Which of the following drug is a disease modifying antirheumatic drug (DMARDs)?

- a. Infliximab
- b. Etanercept
- c. Hydroxychloroquine
- d. Celecoxib

6. Which of the following is not an anti-TNF biologics?

- a. Tocilizumab
- b. Adalimumab
- c. Etanercept
- d. Infliximab



7. Which of the following statement regarding the assessment of Rheumatoid Arthritis (RA) is true?

- a. The American College of Rheumatology Response Criteria includes ACR20, ACR40 and ACR60
- b. The Health Assessment Questionnaire (HAQ) is a radiographic scoring system
- c. DAS is a statistic mathematic calculation developed by EULAR to quantify a single composite score
- d. In modified total sharp score (mTSS), the higher the core, the less severe the radiographic progression is

8. Which of the following is the first approved Janus Kinase (JAK) Inhibitor for the treatment of Rheumatoid Arthritis (RA)?

- a. Axitinib
- b. Tofacitinib
- c. Abatacept
- d. Crizotinib

9. Which of the following statement regarding biologics that are used in Rheumatoid Arthritis (RA) is true?

- a. Biologics is produced by synthetic molecules
- b. The administration method of Biologics is mostly by oral
- c. All classes of biologics carry the safety warning of increased opportunistic infections including tuberculosis
- d. All Biologics will induce neutralizing antibodies

10. Tofacitinib is a _____ oral inhibitor of the Janus Kinase (JAK) family of kinase, including _____ and _____

- a. Selective; JAK2; JAK4
- b. Nonselective; JAK1; JAK3
- c. Selective; JAK1; JAK3
- d. Nonselective; JAK2; JAK4

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 203(D&T)

Cross Sensitivity Reaction of Different Drug Classes

1. A 2. A 3. C 4. C 5. C 6. A 7. B 8. C 9. D 10. C

Over-the-Counter Options for Diarrhea in Children

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ABSTRACT

Children presenting with diarrhea can cause not only concern among parents but may also lead to further complications such as dehydration and decreased absorption of important dietary nutrients. Anti-diarrheal agents have shown to reduce the frequency of stools and overall duration of the condition resulting further decreasing the risk of complications and alleviating the patient's discomfort. This article presents over-the-counter options suitable for younger patients, discusses the differences among them and underlines potential concerns with individual agents.

Keywords: OTC, Children, Anti-diarrheal agents, infection, probiotic, mucoprotective agent, loperamide

INTRODUCTION

Diarrhea is usually a symptom of gastrointestinal infection, which can be caused by a variety of bacterial, viral and parasitic organisms. Common examples include *E. Coli*, Rotavirus, Norwalk agent etc.^(1,2) If the child has access to contaminated food, travelled to regions with epidemics of the mentioned microbial recently, or contacted people with infectious diarrhea, chances are they have contacted the same infection. However other causes of diarrhea are present in infants and children as well such as changing the milk formulation or addition of solid food to the child's diet, and even overfeeding. All these may cause transient diarrhea causing some concern for the parents.^(3,4) Administration of drugs such as antibiotics is another reason which could induce diarrhea as well.⁽³⁾ Additionally, if the baby is lactose intolerant, he/she may also develop diarrhea.⁽⁵⁾ In rare cases, diseases involving gastrointestinal tract such as cystic fibrosis or bile-salt deficiency may be the responsible cause.⁽²⁾ Treatment approaches differ and depend on the cause of diarrhea and its duration. Although a relatively recent bout of loose stools attributed to mild causes may be addressed with over-the-counter options, more severe diarrhea such as if the child's stools contain blood, mucus or pus; if the child has more than 8 stools in 8 hours; or the child has had fever and diarrhea for more than 3 days, should be referred to for immediate medical attention.⁽⁶⁾

OVER-THE-COUNTER PREPARATION FOR DIARRHEA

There are a number of over-the-counter anti-diarrheal agents available in Hong Kong. These include Bioflor, Diatabs Reformulated, Imodium, Imodonl, Kaolin and Pectin Mixture DHA, Kaopectin, Lacteol Fort, Lopa, Loper, Loperamil, Loperax, NT-Diorea, Panfurex, Reuteri, Shin-Biofermin S, and Smecta.⁽⁶⁾ Most of these OTC agents contain loperamide as the active ingredient. However, loperamide containing drugs are not suitable for children younger than 2 years old due to ileus and CNS adverse effects.⁽⁷⁾ Also, children under 3 years of age may be more susceptible to the opioid effects of loperamide.⁽⁸⁾ This means products such as Diatabs Reformulated, Imodium, Imodonl, Lopa, Loper, Loperamil, Loperax, NT-Diorea are not suitable for the young child.

Bioflor, Reuteri and Smecta

Bioflor, Reuteri and Smecta are generally safe to be used in children and are indicated for different diarrheal causes in children and infants. Whether these agents are appropriate for the child depends on her situation. Probiotics such as Bioflor, Reuteri, are recommended to be generally safe and show clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea.^(7,18) According to a randomized clinical study, the median duration of diarrhea was significantly 1 day shorter in the probiotic than in the placebo group.⁽⁹⁾ Moreover, in accordance with another randomized controlled trial, Reuteri could lower relapse rate of diarrhea significantly.⁽¹⁰⁾ Evidence also supports its use for the treatment for antibiotics-induced and infectious diarrhea.⁽¹¹⁾

Bioflor

Bioflor (*Saccharomyces boulardii*) is a probiotic indicated for antibiotic-induced diarrhea.⁽⁹⁾ A study shows a reduction in diarrhea duration when *S.boulardii* was given to children within 72 hours after the onset of acute diarrhea.⁽¹⁰⁾ It rarely causes epigastric disturbances. A box of 10 Bioflor sachets costs HK\$43.⁽⁶⁾ However, there are isolated reports showing a patient who was treated with *S.boulardii* later developed infected fungemia with *S.cerevisiae* including a newborn who was contracted the fungemia as well. Therefore, Bioflor should be used with caution in young infants and newborns.⁽¹⁵⁾

Reuteri

Reuteri (*Lactobacillus reuteri*) is another probiotic and indicated for antibiotic-induced and infectious diarrhea.⁽⁹⁾ *Lactobacillus reuteri* significantly reduced the duration of watery diarrhea as compared with placebo in a randomized clinical trial. In this study, children receiving *L. reuteri* had a significantly lower relapse rate of diarrhea.⁽¹¹⁾ Similarly, it has minimal side effect profile.⁽⁶⁾ A pack of 60 Reuteri chewable tabs costs \$380.⁽⁶⁾

Smecta

Smecta contains dioctahedral smectite, which is an aluminium silicate. It is a mucoprotective agent which is capable of adsorbing toxins, bacteria and rotavirus.⁽¹⁶⁾ Combined data from six randomized-controlled trials showed that smectite significantly reduced the duration of diarrhea compared with placebo.⁽¹⁷⁾ It is used for acute diarrhea, mild or moderate dehydration. In one study, it showed efficacy when used together with Oral Rehydration Solution in children suffering from acute gastroenteritis (without uncontrollable vomiting) with mild and moderate dehydration.⁽¹⁸⁾ It is safe and well tolerated. The development or aggravation of constipation is quite rare as well. As the adsorbent properties of Smecta may interfere with the rates and/or levels of absorption of other substances, it is recommended not to administer any other drugs at the same time as Smecta.⁽⁶⁾ It is supplied in sachet form for oral suspension.⁽⁶⁾

If the diarrhea occurs right after the modification of milk formulation or food content of the child, maintaining hydration of the child may be appropriate until the child tolerates the new food.⁽²⁾ Usually these causes of diarrhea are unlikely causes of serious illness and the child would feel better as soon as their digestive tract gets used to the new diet.⁽¹⁾ However caregivers should be educated to give oral rehydration solution to the child if the child is not drinking enough water to prevent dehydration.⁽¹⁾

CONCLUSION

Regardless of the cause, it is important for pharmacists to remind caregivers to maintain sufficient hydration in the child.^(2,4) Oral rehydration solution is recommended for all types of diarrhea to avoid dehydration especially in children and its benefits of reduced mortality are well supported by clinical evidence.⁽¹⁹⁾ In addition, caregivers should be counseled to monitor for signs and symptoms of dehydration such as little or no urine, dry mouth and feeling thirsty frequently.

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Distinction of the Bulbs of *Fritillariae thunbergii* Miq., *Fritillariae ussuriensis* Maxim and *Fritillariae huperhensis* Hsiao et K.C. Hsia by Concert Techniques

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ABSTRACT

Fritillariae bulbus (FB), known as Beimu in Chinese, is an herb commonly used as antitussive and expectorant in Traditional Chinese Medicine (TCM). There is difficulty in distinguishing the authentic species in herbal markets due to the complexity of its botanical origin and its similar morphology with other species. Therefore, a comparative analysis was undertaken through macroscopic and microscopic characterization and thin layer chromatography (TLC) analysis. The three FB species that were investigated include *Fritillaria thunbergii* Miq., *Fritillaria ussuriensis* Maxim and *Fritillaria hupehensis* Hsiao et K.C. Hsia. The fixed, sectioned, and stained plant materials, as well as its crude powder were studied using bright field microscopy according to the usual microscopic techniques. The results of the microscopic features were systematically and comparatively described and illustrated. The three species have distinct microscopic characteristic differences. The TLC profile was developed to show their different chemical characteristics. The methods employed distinguish clearly the three species; thus, providing specific criteria by which samples of these bulbs can be identified.

Keywords: *Fritillariae* Bulbs, Microscopic techniques, TLC chromatographic Method, Quality Assurance, *Fritillariae thunbergii* Miq., *Fritillariae ussuriensis* Maxim, *Fritillariae huperhensis* Hsiao et K.C. Hsia

INTRODUCTION

Fritillariae Bulbus (FB), known as Beimu in Chinese, is one of the most commonly used herb in Chinese Materia Medica (CMM). It is obtained from the bulbs of several *Fritillariae* species (Liliaceae).⁽¹⁻²⁾ Each species possesses a unique treatment function. It is usually used to relieve cough and reduce phlegm.⁽³⁻⁵⁾ In recent years, due to increasing demand for Beimu, many intraspecific taxa of genus *Fritillariae* have been used as Chinese folk medicine in different local regions in China.⁽⁶⁾ Common people can hardly differentiate the three species namely, *Fritillaria ussuriensis* Maxim (FUB), *Fritillaria thunbergii* Miq. (FTB) and *Fritillaria hupehensis* Hsiao et K.

C. Hsia (FHB). This may influence the quality control and commodities circulation of the CMM "Beimu".⁽⁷⁻⁹⁾

Various taxonomic methods and phytochemical analysis have been established to distinguish different species of *Fritillariae*. Gas Chromatograph (GC) analytical method was used to determine the isosteroidal alkaloids of *Fritillaria*.⁽¹⁰⁾ Chao *et al.* (1993) used High Performance Liquid Chromatography-Ultraviolet (HPLC-UV) method to analyze *Fritillaria* isosteroidal alkaloids in different *Fritillaria* species.⁽¹¹⁻¹³⁾ HPLC analysis coupled with evaporative light scattering detection demonstrated an excellent detection for the analysis of non-chromophoric compounds.⁽¹⁴⁻¹⁵⁾ HPLC-Mass Spectrometry (HPLC-MS) has been used to determine the quality and quantity of the constituents of *Fritillariae* bulbs.⁽¹⁶⁻¹⁷⁾ However, all these methods are very complicated, expensive, and can hardly differentiate the different species because most of them contain similar constituents.⁽¹⁸⁻²¹⁾ In this study, a comparative study employing microscopy combined with TLC profile analysis was performed to differentiate the three FB species respectively.

MATERIALS AND METHODS

Materials

Nine batches of samples were collected from different major production areas in China. The details of each crude drug are given in Table 1. The voucher specimens of standard samples were authenticated by Prof. Zhang Hao (School of Pharmacy, Sichuan University). The above materials were deposited in the Bank of Chinese Materia Medica of City University of Hong Kong.

Apparatus

A Leica RM 3325 Rotary microtome (Leica Instruments, Nussloch, Germany) was used to prepare the transverse sections of the three species materials. An imaging system consisting of a Carl Zeiss Axioplan 2 imaging optical microscope (Carl Zeiss, Oberkochen, Germany) and a Panasonic DMC-FX580 digital camera (Panasonic, Osaka, Japan) was used for photographs acquisition.

Table 1. Source of materials of the three species of <i>Fritillariae Bulbus</i>					
	Batch	Locality	Elevation (m)	Date of collection	Voucher
<i>F. thunbergii</i>	No.1	Nantong, Jiangsu	1400	June,2008	Cheung080615
	No.2	Panan, Zhejiang	1150	June,2008	Cheung080623
	No.3	Dongyang, Zhejiang	1500	July,2008	Cheung080702
<i>F. hupehensis</i>	No.1	Enshi, Hubei	1800	July,2009	Wang20090720
	No.2	Lichuan, Hubei	1760	June,2009	Wang20090630
	No.3	Enshi, Hubei	1700	July,2009	Wang20090707
<i>F. ussuriensis</i>	No.1	Tonghua, Jilin	1450	June,2008	Cheung20080628
	No.2	Baishan, Jilin	1500	July,2008	Cheung20080715
	No.3	Tieli, Heilongjiang	1300	July,2008	Cheung20080725

Reagents

FAA (formalin, glacial acetic acid, and 70% ethanol in the ratio of 0.5:0.5:9.0 parts, respectively) and a gradual ethanol series from 50 to 95%, (Uni-chem, England) were prepared for the specimen fixation and dehydration, respectively. A Safranin and fast green (Aldrich, America), solution was prepared for specimen staining, respectively. Chloral hydrate, and diluted glycerin (Uni-chem, England), were prepared according to procedures described in Appendix XV of the pharmacopoeia of the People's Republic of China (The State Pharmacopoeia Committee of China, 2010). Xylene (LAB-SCAN, Thailand), paraffin wax, and Canadian balsam (Serva: feinbiochemica Heidelberg, NY). Pre-coated silica gel plates with concentrating zones (5×10 cm) (Merck, Darmstadt, Germany), was used without any pretreatment. The mobile phase was Dichloromethane: Ethyl acetate: Methanol: diethylamine (6:3:0.3:0.5). All chemical and solvents were of analytical grade. Hupehenine, Peimine, Peinine were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).

Macroscopic Characteristics of Crude Drugs

The gross external features of each sample were examined by observing, measuring, touching, smelling, and tasting. The color digital photographs were taken with a digital camera Nikon D90.

Microscopic Characteristics of the Powdered Crude Drugs

The dried materials were softened in the boiled water and cut into appropriate sizes and fixed in FAA for 48 hours. Samples were treated through the gradual ethanol and xylene sequence, embedded in paraffin, and sectioned on a microtome in slices 12 μm thickness. Tissues were stained by safranin and the fast green solution, and finally mounted in Canada balsam for observation. Some sections were not stained so that idioblasts and other deposits would not be destroyed or otherwise altered during processing. The samples of crude drug were powdered and passed through a 250 μm sieve. Ten different slides from the same powder were observed. The three batches of samples per species were studied to reveal and validate the key authentication parameters. The values of various cells and tissues were obtained by taking at least 25 measurements for each species. All representative microscopic features were recorded by digital color photography.

TLC Profile of Three FB Species

Two grams of the powdered sample were placed into a 50-mL centrifugal tube. Two mL of ammonium hydroxide solution and 10 mL of ethanol were added into it. Then the mixture was sonicated (90 W) for 15 min. The supernatant was filtered to obtain the test solution. Standard solutions containing 0.2 mg/ml⁻¹ of Hupehenine, Peimine, and Peinine in methanol were freshly prepared before use. A 2 μl loading of each standard and 10 μl sample solution was spotted on the TLC plate with concentrating zone by means of a Nanomat III. The chromatogram was allowed to develop during 20 min to a height of about 90 mm in a twin-trough chamber previously saturated with the mobile phase. Then, the plate was removed and sprayed evenly with 10% sulfuric acid and it was heated at about 105°C for 3 min. The image of the TLC plate was immediately examined under UV light (366 nm).

RESULTS

In order to distinguish the three FB species, detailed examination of macroscopic and microscopic features with phytochemical TLC analysis have been performed.

External Morphology

***F. Thunbergii*:** The drug is classified according to its sizes. The larger one is removed from the central bud and commonly known as "Dabei". The smaller one, which is not removed from the central bud is commonly known as "Zhubei".

Dabei is the outer single scale leaf of the bulb, slightly crescent shape, 1.1-2.1 cm high, and 1-4.5 cm in diameter. The outer surface is whitish to pale yellow and the inner surface is white to pale brown. Both the two surfaces were covered with white powder. The texture is hard, fragile, and easily broken. Its structure is white to yellowish-white, and highly starchy. The taste is slightly bitter.

Zhubei is the whole bulb, it is oblate, 0.9-2.1 cm high, and 1.1-3.5 cm in diameter. The outer surface is whitish. It consists of 2 outer scale leaves which are plump, fleshy, and slightly in reniform shape. The two scale leaves are attached to each other. It contains 2-3 small scale leaves and dried shrunken stem in the center (Fig. 2A).

The Morphology of FHB and FUB are similar to FTB except that their sizes and the color of the surfaces are different. FHB is 0.6-1.9 cm high, 0.8-3.7 cm in diameter while FUB is 0.5-1

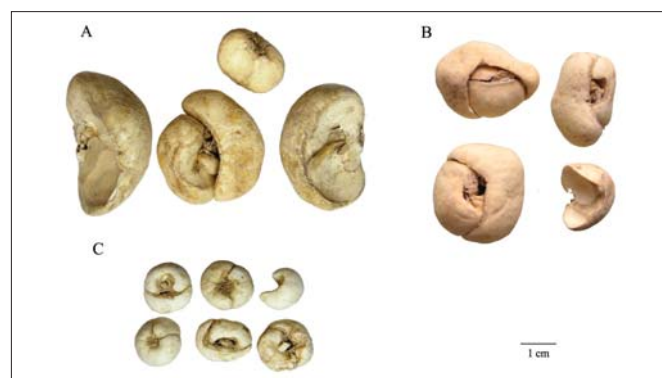


Figure 1: Macroscopic features of the bulbs of *Fritillaria thunbergii* Miq. (A) and *Fritillaria hupehensis* Hsiao et K. C. Hsia (B), *Fritillaria ussuriensis* Maxim (C)

cm high, 0.6-2 cm in diameter. They were not classified as to “Dabei” and “Zhubei” according to their size because FHB and FUB were smaller than FTB based on the size. The surface of FUB is milky white to pale yellowish-white and shallower than FHB and FTB. However, the surface of FHB is sometimes pale brown and deeper than FUB and FTB.

Microscopic Identification of Transverse Section

F. thunbergii: The transverse section is crescent shape in outline. The upper epidermis of its scale leaves consists of 3-7 layers of cell while the lower epidermis consists of 2-4 rows of cell. The outer wall is thickened with cuticle. Occasionally, the crystals of calcium oxalate are visible in the epidermal cells. The vessels are small and scattered in parenchyma tissue. Parenchymatous cells are filled with starch granules (Fig. 2B). The microscopic characteristics of transverse sections of FHB and FUB are similar to FTB. However, there are some different characteristics according to the cell layers, the size of epidermis, the size of parenchyma cells, and the size of the crystals. Photos of the transverse section of rhizomes are shown in Figure 2. The details of the microscopic characteristics of the bulbs of all species are presented in Table 2.

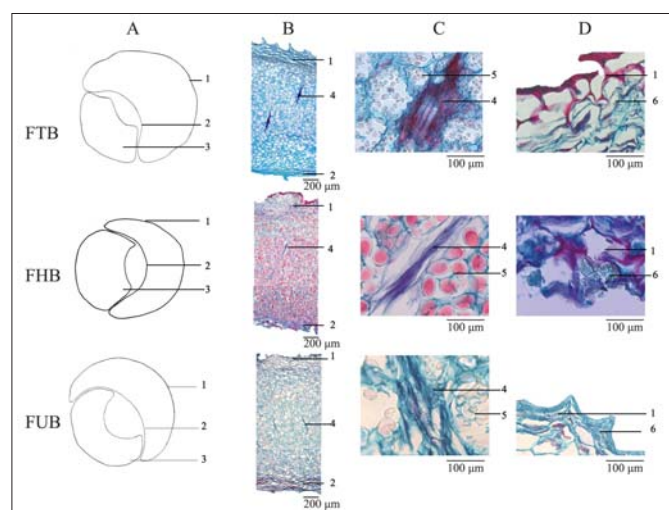


Figure 2: Microscopic Features of the Transverse Section of the Bulbs of FTB, FHB and FUB. A: Simple sketch of transverse section of the bulb; B: Outline of transverse section of the bulb; C: Details of vessels in parenchyma cells; D: Epidermis of the bulb. 1 = upper epidermis; 2 = lower epidermis; 3 = leaf scale; 4 = vessels; 5 = starch granules; 6 = crystal of calcium oxalate

Microscopic Identification of Powder

F. thunbergii: The color of the powder is grayish white. Starch granules are numerous, containing simple granules and compound granules. The simple granules are ovoid, broad-ovoid or elliptical, 5-52 μm in diameter, hilum shows pointed, cleft-like or V-shaped in the smaller end, its striations can be observed. Compound granules are rare. Crystals of calcium oxalate are rare, minute and mostly granular, sometimes it is in fusiform, square or thin bacilliform. Anticlinal walls are slightly crooked and beaded-thickened; stomata is rounded or depressed rounded and consists of 4-5 subsidiary cells in its rim. The size of the stomata is 50-58 μm in diameter, but it can be occasionally visible.

The histological characteristics of the diagnostic elements occurring in the drug powders of other two species are similar to FHB except that the size and shape of starch granules, the size of crystal as well as vessels are different. It was found

out that some starch granules of FUB are short, claviform in shape and there is no pointed hilum which is different from the other two species. The comparison of the powder of the three species is described in Table 3. Photos of the powders are shown in Figure 3.

	Size of upper epidermis cell (μm)	Layers of upper epidermis	Size of lower epidermis cell (μm)	Layers of lower epidermis	Size of parenchyma cells (μm)
FTB	15-51*43-85	3-7	29-50*78-116	2-4	47-72*76-122
FHB	10-46*35-75	3-5	22-46*54-92	2-4	44-84*53-98
FUB	80-195*21-47	4-8	17-25*43-65	2-7	63-89*81-140

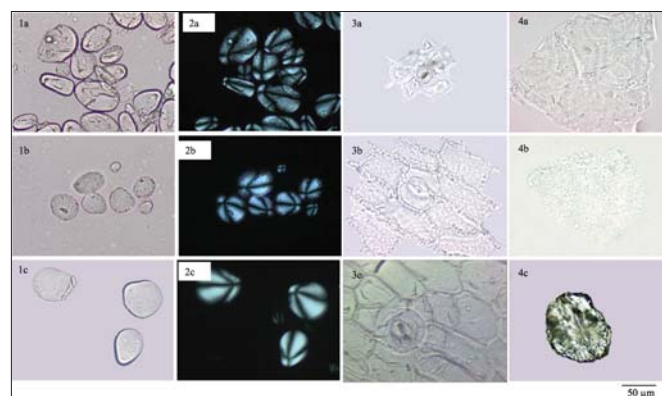


Figure 3: Microscopic Features of the Powder of FTB, FHB and FUB. a = FTB; b = FHB; c = FUB. 1 = starch granules under the light microscopy; 2 = starch granules under the polarized microscopy; 3 = stoma; 4 = crystal of calcium oxalate

	Color	Starch granules			Crystal	
		Shape	Size	Hilum	Shape	Size
FTB	Grayish white	ovoid, broad-ovoid or elliptical	5-52 μm	pointed, cleft-like, V-shaped	rare, minute, mostly granular, some in fusiform, square or thin bacilliform.	2-20 μm
FHB	Off-white to pale brown	Broad-ovoid, long ellipsoid or sub-spheroid	11-70 μm	pointed, cleft-like or V-shaped	Sub-square, rhombic, granular or clustered	20-117 μm
FUB	Whitish	ovoid, triangular-ovoid, short claviform	5-52 μm	cleft-like, V-shaped	Minute, sub-square	5-24 μm

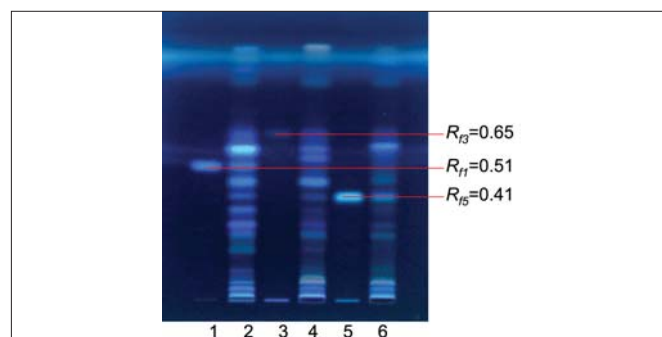


Figure 4: TLC Profile of the Tested Markers and FB. (Lane 1 = Hupehenine; 2 = Fritillaria hupehensis Hsiao et K. C. Hsia; 3 = Peimine; 4 = Fritillaria thunbergii Miq.; 5 = Peimine; 6 = Fritillaria ussuriensis Maxim)

Analysis of the three FB species by TLC method

Thin Layer Chromatography plates are pre-coated plates

of silica gel 60 F254 (E. merck) of uniform thickness of 0.2 mm. The marker compounds (1,3,5) and the ethanol extracts of the three FB species were subjected to TLC analysis to develop profile patterns that qualify the marker compounds. It was found in Fig. 4 that a mixture of Dichloromethane: Ethyl acetate: Methanol :diethylamine (6:3:0.3:0.5 v:v:v:v) gave a good separation band. The R_f value were 0.51, 0.65 and 0.41 for compounds 1, 3 and 5, respectively. The three FB species differed significantly and showed different characteristic patterns (Fig 1). It also demonstrated that if only marker compound 1 is found to be present in the sample, then it is FHB. If both marker compounds 3 and 5 are present, then it is either FUB or FTB. At this point, macroscopy and microscopy is necessary in distinguishing these two species.

DISCUSSION

The results of the study showed that the established morphological, microscopic characteristics, and TLC method are suitable for the authentication of three *Fritillariae* bulbs. The results provide some reference data for its quality control and safe application. The comparative macroscopic and microscopic observations of plant organs, tissues and crude drug powder of the three species of *Fritillariae* indicate that many of these anatomical characteristics are homologous. Accordingly, a generalized description to account for these similarities was drawn. For instance, its epidermis is made up of several layers of cells containing some crystal of calcium oxalate. Parenchyma tissue cells are filled with starch grains. Vessels are small and existed among the parenchyma cells.

However, the different *Fritillaria* species possesses the unique microstructural characteristics. In the previous study, there is limited literature that mentioned the detailed microscopic identification of the transverse section of *Fritillariae* bulbs. On the other hand, it was found out in this study that the calcium oxalate crystals that existed in the epidermis is varying significantly in terms of size. Those found in FHB are bigger than others. The outer walls of the epidermises of FTB and FHB were thickened with cuticle while that of FUB showed some sinuate protuberance. This study provides detailed microscopic information for the authentication of the three diverse species of *Fritillariae*. The TLC profile indicates the chemical characteristics of the three FB species. FHB can be distinguished among others by marker compound 1. Although FTB and FUB cannot be distinguished by compound markers 1, 2 and 3, it has been shown that the developed profile bands are significantly different.

CONCLUSION

Therefore, the result of this experiment can be utilized as a standard for identification of the three *Fritillaria* species whether the plant materials are powdered and mixed. Further studies on the pharmacologic and physiologic effects of the chemical compounds present in *Fritillaria* species are highly recommended to ensure safety and efficacy.

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Author's background

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Concert Approach to the Authentication, Qualitative Evaluation and Bioactivity Assessment of Beimu

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Botanical Species: *Fritillaria cirrhosa* D. Don, *Fritillaria unibracteata* Hsiao et K.C. Hsia, *Fritillaria przewalskii* Maxim, *Fritillaria delavayi* Franch, *Fritillaria thunbergii* Miq., *Fritillaria ussuriensis* Maxim, *Fritillaria hupehensis* Hsiao et K.C. Hsia, *Fritillaria pallidiflora* Schreb

Plant Family: Liliaceae / Fritillaria

Pharmacopoeia Name: Fritillaria Bulbus

Chinese Name: 川貝母 (Chuan-Beimu, 卷葉貝母, 暗紫貝母, 甘肅貝母, 棱砂貝母), 浙貝母 (Zhe-Beimu), 平貝母 (Ping-Beimu), 湖北貝母 (Hupe-Beimu), 伊貝母 (Yi-Beimu)

Other Names: Chuan-Beimu (川貝母) includes 虻, 黃虻, 空草, 貝母, 貝父, 葯實, 苦花, 苦菜, 勤母; Zhe-Beimu includes: 土貝母, 象貝, 象貝母, 浙貝, 大貝母 and Thunberg fritillary.

Part usually Used: bulb of the plant

ABSTRACT

Beimu, which was first recorded more than two thousand years ago as a medium-grade medicinal material in Shen Nong Ben Cao Jing, is the dried bulb of *Fritillaria cirrhosa* D. Don (chuan-bemu), *F. thunbergii* Miq. (zhe-beimu), *F. ussuriensis* Maxim (pin-beimu) or other officially endorsed species of *Fritillaria* genus. These bulbs are botanical source for various pharmaceutical active components. The bulbs of genus *Fritillaria* all contain cervine-type steroidal alkaloid, which possess anti-tussive, anti-coughs, sedative and antibacterial activities. Their contents, biological effects and prices, however, vary significantly. Hence, deliberate or unintentional adulteration of beimu is common in the market. This article reviews some information and methods with aims to differentiate each species. Based on the data of their morphological traits and analysis of chemical profile, all these species could be authenticated and their quality could be determined. Hence, their benefits to health could be maximized.

Keywords: Beimu, *Fritillaria* genus, steroidal alkaloids, morphological traits, TLC methods, LC fringerprint, biological effects, quality assurance

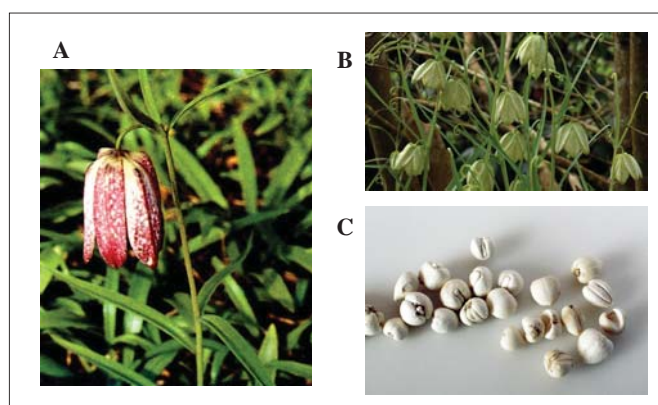
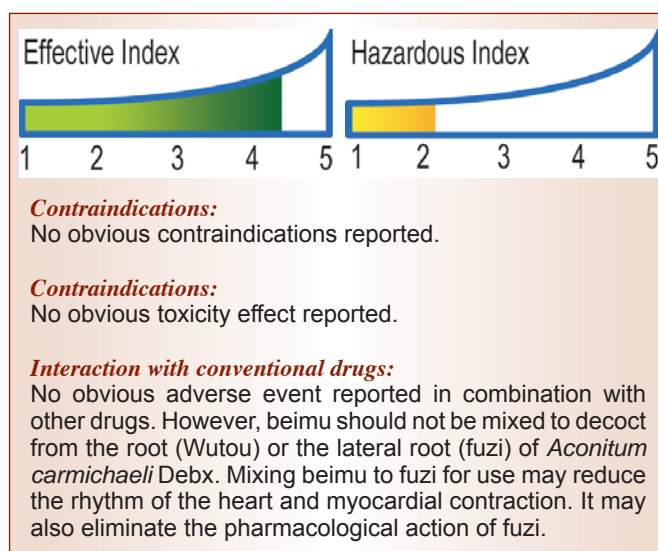


Figure 1: Plant of (A) *Fritillaria cirrhosa* D Don (A), (B) *F. thunbergii* Miq. and (C) Typical appearance of the bulbs of Chuanbeimu.



INTRODUCTION

The genus *Fritillaria* is a botanical source for many bioactive components. It is a genus of perennial herbs widely distributed in Mediterranean Region, North America and Central Asia at sub-tropical weather (Table 1). From the list, it is not difficult to imagine how complex are they and their authentication is so easy.

Table 1. List of *Fritillaria* species identified or reported in literature by far.

• <i>Fritillaria acmopetala</i> – Lebanese fritillary	• <i>Fritillaria affinis</i> – checker lily, chocolate lily
• <i>Fritillaria agrestis</i> – stinkbells	• <i>Fritillaria anhuiensis</i> S.C.Chen & S.F.Yin
• <i>Fritillaria armena</i> Boiss.	• <i>Fritillaria assyriaca</i>
• <i>Fritillaria atropurpurea</i> – purple fritillary, spotted fritillary, spotted mountainbells, spotted missionbells	• <i>Fritillaria camschatcensis</i> – Kamchatka fritillary, rice lily, skunk lily, outhouse lily, dirty diaper, chocolate lily, Indian rice
• <i>Fritillaria brandegei</i> Eastw.	• <i>Fritillaria biflora</i> – chocolate lily
• <i>Fritillaria caucasica</i> Adams	• <i>Fritillaria cirrhosa</i> D.Don
• <i>Fritillaria conica</i> Boiss.	• <i>Fritillaria crassicaulis</i> S.C.Chen
• <i>Fritillaria crassifolia</i> Boiss. & A. Huet	• <i>Fritillaria dagana</i> Turcz. ex Trautv.
• <i>Fritillaria dajinensis</i> S.C.Chen	• <i>Fritillaria davidii</i> Franch.
• <i>Fritillaria davisii</i> Turrill	• <i>Fritillaria delavayi</i> Franch.
• <i>Fritillaria drenovskii</i> Degen & Stoj.	• <i>Fritillaria dzhabavae</i> A.P.Khokhr.
• <i>Fritillaria eastwoodiae</i> – Butte County fritillary, Eastwood's fritillary	• <i>Fritillaria eduardii</i> Regel
• <i>Fritillaria ehrhartii</i> Boiss. & Orph.	• <i>Fritillaria elwesii</i>
• <i>Fritillaria epirotica</i> Turrill ex Rix	• <i>Fritillaria euboica</i> Rix
• <i>Fritillaria falcata</i> – talus fritillary	• <i>Fritillaria fusca</i> Turrill
• <i>Fritillaria gentneri</i> – Gentner's fritillary	• <i>Fritillaria gibbosa</i> Boiss.
• <i>Fritillaria glauca</i> – Siskiyou fritillary, Siskiyou missionbells	• <i>Fritillaria graeca</i>
• <i>Fritillaria grandiflora</i> Grossh.	• <i>Fritillaria grayana</i> Reichenb.f. & Baker
• <i>Fritillaria gussichiae</i> (Degen & Dörf.) Rix	• <i>Fritillaria hispanica</i>
• <i>Fritillaria imperialis</i> – kaiser's crown, crown imperial	• <i>Fritillaria involucrata</i> All.
• <i>Fritillaria karelinii</i> Fischer ex D.Don	• <i>Fritillaria kotschyana</i> Herb.
• <i>Fritillaria kurdica</i> Boiss. & Noë	• <i>Fritillaria latifolia</i> Willd.
• <i>Fritillaria liliacea</i> – fragrant fritillary	• <i>Fritillaria lusitanica</i> Wikstr.
• <i>Fritillaria lutea</i> Mill.	• <i>Fritillaria macedonica</i> Bornm.
• <i>Fritillaria maximowiczii</i> Freyn	• <i>Fritillaria meleagris</i> – snake's head fritillary, checkered daffodil, frog-cup, Guinea-hen flower, leper lily, kockavica (Croatian)
• <i>Fritillaria meleagroides</i> Patrin ex Schult.f.	• <i>Fritillaria messanensis</i> Raf.
• <i>Fritillaria michailovskiyi</i> Fomin	• <i>Fritillaria micrantha</i> – brown fritillary, brown bells
• <i>Fritillaria monantha</i> Migo	• <i>Fritillaria montana</i> Hoppe
• <i>Fritillaria obliqua</i> Ker Gawl.	• <i>Fritillaria ojaiensis</i> – Ojai fritillary (sometimes included in <i>F. affinis</i>)
• <i>Fritillaria olgae</i> Vved.	• <i>Fritillaria ophioglossifolia</i> Freyn & Sint.
• <i>Fritillaria orientalis</i>	• <i>Fritillaria pallidiflora</i>
• <i>Fritillaria persica</i> – adiyaman (Turkish)	• <i>Fritillaria pinetorum</i> – pinewoods fritillary, Davidson's fritillary
• <i>Fritillaria pluriflora</i> – adobe lily	• <i>Fritillaria pontica</i> Wahlenb.
• <i>Fritillaria przewalskii</i> Maxim.	• <i>Fritillaria pudica</i> – yellow fritillary, yellowbells
• <i>Fritillaria purdyi</i> Eastw.	• <i>Fritillaria pyrenaica</i>
• <i>Fritillaria raddeana</i> Regel	• <i>Fritillaria recurva</i> – scarlet fritillary
• <i>Fritillaria regelii</i> Losinsk.	• <i>Fritillaria rhodia</i> A.Hansen
• <i>Fritillaria rhodocanakis</i> Orph. ex Baker	• <i>Fritillaria roylei</i>
• <i>Fritillaria ruthenica</i> Wikstr.	• <i>Fritillaria sewerzowii</i> Regel
• <i>Fritillaria sichuanica</i> S.C.Chen	• <i>Fritillaria sinica</i> S.C.Chen
• <i>Fritillaria skorpii</i> Velen.	• <i>Fritillaria striata</i> – striped adobe lily
• <i>Fritillaria sibirnyi</i> Velen.	• <i>Fritillaria taipaiensis</i> P.Y.Li
• <i>Fritillaria tenella</i>	• <i>Fritillaria thunbergii</i> Miq.
• <i>Fritillaria tortifolia</i> X.Z.Duan & X.J.Zheng	• <i>Fritillaria tubiformis</i> Gren. & Godr.
• <i>Fritillaria tuntasia</i> Helder. ex Halácsy	• <i>Fritillaria unibracteata</i> P.K.Hsiao & K.C.Hsia
• <i>Fritillaria uva-vulpis</i>	• <i>Fritillaria ussuriensis</i> Maxim.
• <i>Fritillaria verticillata</i>	• <i>Fritillaria viridea</i> Kellogg
• <i>Fritillaria walujewii</i> Regel	• <i>Fritillaria yuminensis</i> X.Z.Duan
• <i>Fritillaria yuzhongensis</i> G.D.Yu & Y.S.Zhou	

Beimu (貝母) is the bulbs of various *Fritillaria* species and has been used as one of the most important folk medicines for thousands of years.^(1,2) The bulb, comprising of 2 scales, is spherical or broadly ovate ranging from 0.5 cm to 3.5 cm in diameter. Leaf of this genus normally grows opposite; a few grown in middle and upper (Figure 1). The plant requires full sun or partly shaded for growth in loamy, well-drained, moisture retentive and humus rich soil.

In the 2010 edition of Chinese Pharmacopoeia, a total of five groups of Beimu (all together nine *Fritillaria* species), namely Zhe-Beimu (*F. Thunbergii* Miq.), Chuan-Beimu (*F. cirrhosa* D. Don, *F. unibracteata* Hsiao et K. C. Hsia, *F. Przewalskii* Maxim. ex Batal. and *F. delavayi* Franch.), Ping-Beimu (*F. Ussuriensis* Maxim.), Hubei-Beimu (*F. hupehensis* Hsiao et K. C. Hsia) and Yi-Beimu (*F. walujewii* Regel and *F. pallidiflora* Schrenk), all together nine species were officially recommended for use in Chinese medicines.⁽³⁾

Due to the complexity of botanical origin, it is quite common to find falsely labeled *Fritillaria* in herbal markets. The adulteration of *Fritillaria* sometime is conducted purposely for economic reasons, as the price of *Fritillaria* vary remarkably in markets. Therefore, the development of quality control protocols for qualitative and quantitative determination of alkaloids in *Fritillaria* is an essential issue for the effective and safe clinical use of this herbal medicine. In this study, we review five of the most common Beimu, compared the macro and microscopic features, summarize the analytical methods and bioactive properties.

MORPHOLOGICAL DESCRIPTION AND IDENTIFICATION

Morphological features and differences

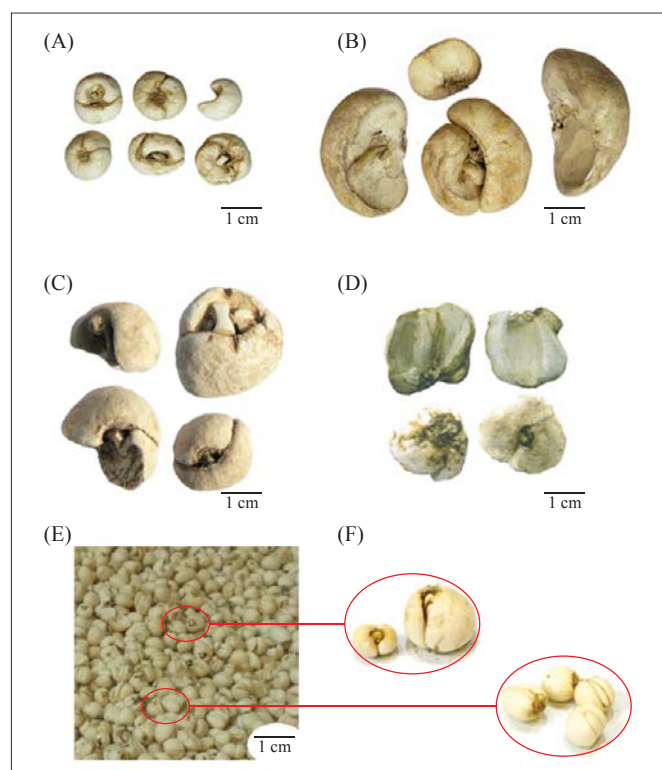


Figure 2: The morphological appearance of different Beimu. (A) Ping-beimu; (B) Zhe-beimu; (C) Hubei-beimu; (D) Yi-beimu; (E) Chuan-beimu; (F) magnified figures of the “guanyinbaozi” (red) and the “huanzhongbaoyue” (black) .

Fritillariae Ussuriensis Bulbus (Ping-beimu, 平貝母) (Figure 2A)
It is oblate in shape, 0.5-1 cm high, 0.8-2.0 cm in diameter. It is externally milky white to pale yellowish-white. The outer scale leaves are plump, uniform in size or the large scale leaf embracing the smaller one, the apex is slightly flat or dented, frequently slightly split, the scale leaf in the centre smaller and its bottom is flat. The texture is hard and fragile, fracture starchy. Odour of the bulbs is slight but taste bitter.

Fritillariae Thunbergii Bulbus (Zhe-beimu, 浙貝母) (Figure 2B)
Dabei

The bulb is enclosed by an outer single scale leaf, slightly crescent-shaped, 1.1-2.1 cm high, 1.0-4.5 cm in diameter. The outer surface is whitish to pale yellow, the inner surface is white or pale brown, covered with white powder. Texture is hard and fragile, easily broken; fracture white to yellowish-white, highly starchy. The odor is slight; taste slightly bitter.

Zhubei

The whole bulb is oblate, 0.9-2.1 cm high, 1.1-3.5 cm in diameter. It is externally whitish, and the 2 outer scale leaves plump and fleshy, slightly swelling in shape, held to each other, enclosing 2-3 small scale leaves and remains of the dried shrunken stem.

Fritillariae Hupehensis Bulbus (Hubei-beimu, 湖北貝母) (Figure 2C)

The bulbs are oblate, 0.4-2.3 cm in height, 0.8-3.7 cm in diameter. The outer surface is off-white to pale brown, the outer scale leaves are fleshy, nearly reniform, or vary considerably in size, the large scale closely embracing the small one, the apex is closed or open, with 2-6 scales and shrunken stem remains. The inner surface is yellowish to whitish. Base depressed, with remains of whitish to brownish epidermis and a few fibrous roots. The single scale leaf appears swelling-shoe-shaped, 0.7-3.2 cm in length, 0.4-1.8 cm in diameter. The texture is fragile, fracture whitish, starchy. The odour is slight; taste, bitter.

Fritillariae Pallidiflorae Bulbus (Yi-beimu, 伊貝母) (Figure 2D)

It is conical, relatively large, 1.2-3.5 cm high, 1.0-3.0 cm in diameter. It is externally pale yellowish-white to whitish, slightly rough. The outer scale leaves are cordate, plump and large, almost equal size and embraced together. The apex is slightly

acute, seldom crackable; base slightly concave, with remnants of stem and bud inside. The texture is hard and fragile; fracture white, highly starchy. The odour is slight; taste slightly bitter.

Fritillariae Cirrhosae Bulbus (Chuan-beimu, 川貝母) (Figure 2E)

The bulb is subconical or subspherical, some nearly oblate. Its size is about 0.3-1.4 cm high, 0.4-1.6 cm in diameter. The color is externally whitish. The outer scale leaves vary considerably in size, with the large scale closely embracing the small one, the uncovered part appearing crescent, commonly known as "Huaizhong Baoyue" (holding the moon in the arms) (Figure 2F). The apex is closed, with subcylindrical and slightly tapering buds and 1-2 small scales inside; apex obtuse or slightly acute, base even and slightly concave, with a greyish-brown disk at central part, remains of fibrous roots occasionally found. The texture is hard and fragile, fracture white, starchy. The odour is slight; taste slightly bitter.

The differences between different Beimu described above are compared and summarized in Table 2. From this table, it could be found that chuan-beimu, in general, is the smallest while Zhe-mubei is the largest.

Microscopic features of the bulbs

The important features of both the transverse section and the powder of Beimu, including Zhe-beimu, Ping-beimu, Hubei-beimu, and Yi-beimu, are shown in Figure 3, 4 and Table 3. The microscopic features of each type of Beimu in the aspect of the upper epidermis, lower epidermis, cell wall, crystal of calcium oxalate, parenchyma cells, color, starch granules, hilum, compound granules, crystals of calcium oxalate, vessels, epidermal cells, stomata are compared.

CHEMICAL COMPONENTS

The main constituents in Beimu are isosteroidal alkaloids, including verticine, verticinone, isovericine, ebeiedine, ebeiedinone, and so on.^(4,5) In addition, some non-alkaloid constituents, such as saponin, terpenoids, steroids, succinic

Species	Shape	Hight	Diameter	Outer surface	Apex	Base
Chuan-beimu (川貝母) (Includes <i>Fritillaria cirrhosa</i> D. Don; <i>F. unibracteata</i> Hsiao et K.C. Hsia; <i>F. przewalskii</i> Maxim, <i>F. delavayi</i> Franch)	Subconical or subspherical	0.3-1.4 cm	0.4-1.6 cm	whitish	Closed, with subcylindrical and slightly tapering buds and 1-2 small scales inside	Even and slightly concave with a greyish-brown disk at central part, remains of fibrous roots occasionally found.
Hubei-beimu (湖北貝母) (<i>Fritillaria hupehensis</i> Hsiao et K.C. Hsia)	oblate	0.4-2.3 cm	0.8-3.7 cm	Off-white to pale brown	Closed or open, with 2-6 scales and shrunken stem remains	Depressed, with remains of whitish to brownish epidermis and a few fibrous roots
Ping-beimu (平貝母) (<i>Fritillaria ussuriensis</i> Maxim)	oblate	0.5-1.0 cm	0.8-2.0 cm	Milky white to pale yellowish- white	Slightly flat or dented, frequently slightly split	Flat
Yi-beimu (伊貝母) (<i>Fritillaria pallidiflora</i> Schreb)	Conical	1.2-3.5 cm	1.0-3.0 cm	Pale yellowish- white to whitish, slightly rough	Slightly acute, seldom crackable	Slightly concave, with remnants of stem and bud inside
Zhe-beimu (浙貝母) (<i>Fritillaria unibracteata</i> Hsiao et K.C. Hsia)	Dabei	oblate	1.1-2.1 cm	1.0-4.5 cm	Whitish to pale yellow	
	Zhubei	oblate	0.9-2.1 cm	1.1-3.5 cm	Whitish	

acid, thymidine, adenosine, have also been identified in different *Fritillaria* species.⁽⁶⁾ Various chemical and pharmacological studies on Beimu have revealed that the major biologically active ingredients to relieve cough in the bulb are alkaloids with their types and contents varying in different *Fritillaria* species.⁽⁷⁾

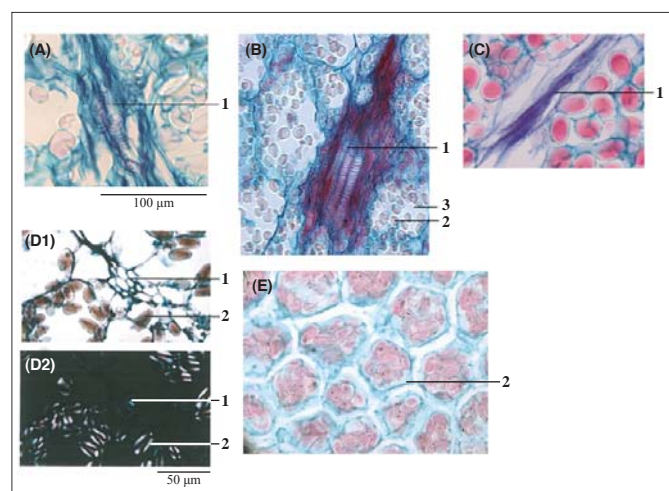


Figure 3: Microscopic features of the transverse section of different Beimu. (A) Ping-beimu; (B) Zhe-beimu; (C) Hubei-beimu; (D) Yi-beimu; (E) Chuan-beimu. 1 = Vessel, 2 = Starch granule, 3 = Parenchyma cell.

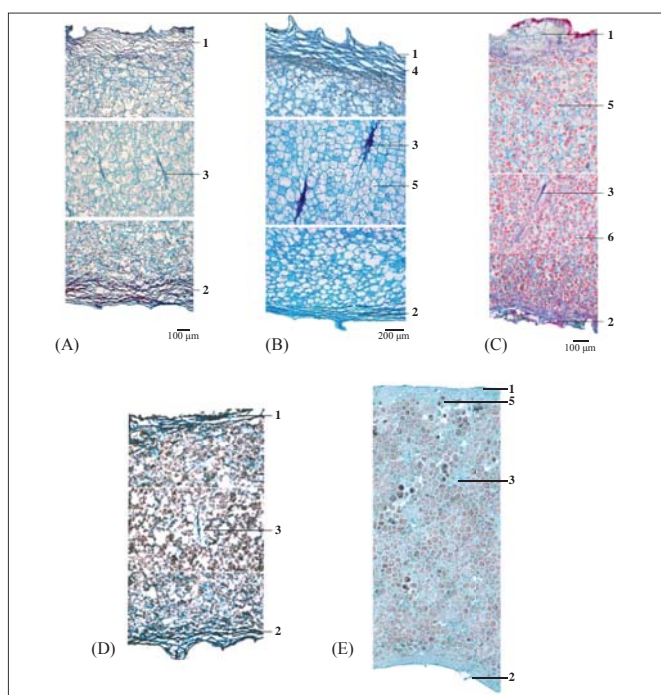


Figure 4: Microscopic features of transverse section of Beimu. (A) Ping-beimu; (B) Zhe-beimu; (C) Hubei-beimu; (D) Yi-beimu; (E) Chuan-beimu. 1 = Upper epidermis, 2 = Lower epidermis, 3 = Vessels, 4 = Crystals of calcium oxalate, 5 = Parenchyma cell, 6 = Starch granules.

Table 3. Comparison of some distinguishing features between different species of Beimu.						
Distinguishable Features		Zhe-beimu	Ping-beimu	Hubei-beimu	Yi-beimu	Chuan-beimu
Transverse section	Upper epidermis	3-7 rows of cells	4-8 layers of cells	3-5 layers of cells	1-5 layers of cells	1 layer of cells, sub-square or sub-rectangular
	Lower epidermis	2-4 rows of cells	2-7 layers	2-4 layers	2-8 layers of cells	-
	Cell wall	Thickened with cuticle.	Slightly thickened, some with sinuate protuberance	Thickened with cuticle.	Some showing nipple-like protuberances.	-
	Crystal of calcium oxalate	Visible in epidermal cells	Visible in epidermal cells	Sometimes visible in epidermal cells.	Present	-
	Parenchyma cells	Replete with starch granules	Filled with starch granules	Filled with starch granule	Occupies the major portion of the scale leaf, willed with starch granules	Sub-rounded, filled with starch granules
Powder	Color	Greyish-white	Whitish	Off-white to pale brown.	Whitish.	Whitish or pale yellow
	Starch granules	Numerous. Ovoid to broadly ovoid or ellipsoid, 5-52 µm in diameter.	Simple, ovoid to triangular-ovoid or short-claviform, 5-52 µm in diameter.	Fairly abundant, broadly ovoid, long ellipsoid or subspheroid, 10-70 µm in diameter.	Extremely numerous, mostly simple, broad-ovoid, triangular-ovoid, subconchoidal or irregular-ovoid, 6-60 µm in diameter.	Fairly abundant, broadly ovoid, long spheroidal or irregularly spheroidal, some with uneven or slightly branch-like edges, 5-64 µm in diameter.
	Hilum	Pointed, cleft-like or V-shaped in the narrowed end, striations visible.	Cleft-like, pointed or V-shaped at the narrow end, striations dense and distinct.	Pointed, V-shaped, slit-shaped or separated to be like horstail, striations fine and dense, distinct.	Indistinct, striations distinct, black and cruciate-shaped under the polarized microscope.	Short slit-shaped, pointed, V-shaped or Ushaped, and faint striations visible.
	Compound granules	Rare	Rare	Consisting of 2-3 components, smaller, visible occasionally.	-	-
	Crystals of calcium oxalate	Rare, minute, mostly granular, some have fusiform, square or thin bacilliform shape	Minute, polychromatic under the polarized microscope	Rhombic, subsquare, granular or clustered, 20-118 x 5-52 µm in diameter.	Rare, finely fusiform, columnar or granular, bright white or polychromatic under the polarized microscope.	-
	Vessels	Most spiral, 3-16 µm in diameter.	-	Spiral	Spiral or reticulate, 15-50 x 5-52 µm in diameter.	Spiral, 5-46 µm in diameter.
	Epidermal cells	Subpolygonal or rectangular, anticlinal wall slightly crooked and beaded-thickened	Subrectangular, semi-square or strip-shaped in surface view, 80-195 µm long and 21-47 µm wide.	Subsquare or polygonal, anticlinal walls irregularly beaded.	Subrectangular in surface view.	Subrectangular, anticlinal walls sinuous, rounded or oblate.
	Stomata	Less visible, subrounded or depressed-rounded, 50-58 µm in diameter, with 4-5 subsidiary cells	Depressed-rounded, 40-50 µm in diameter, with 4-6 subsidiary cells.	Occasionally visible, oblate, with 4-5 subsidiary cells	Obscurely visible, subrounded, 40-60 µm in diameter, with 4-7 subsidiary cells.	Occasionally found.

A wide range of structural variation of steroidal alkaloids has been reported in the *Fritillaria* species, which differs in terms of the number, position, and nature of the functional groups. Based on the basic structural skeleton, the alkaloids in *Fritillaria* can be divided into three major types, including cevanine, jervinine and veratramine.⁽⁶⁾ In the nine *Fritillaria* species officially used in China as the plant sources for Beimu, various chemicals have been identified and the major alkaloids are puqienine F, imperialine-3- β -d-glucoside, puqienine C, puqienine D, imperialine, peimisine, verticine N-oxide, puqienine E, puqiedine-7-ol, hupeheninose, puqietinonose, verticine, verticinone N-oxide, yibeinose A, verticinone, puqienine B, puqienine A, isovericine, puqietinone, ebeiedinone, N-demethylpuqietinone, puqiedinone, ebeienine, ebeiedine, puqiedine, and puqietinedinone. Structures of these major ingredients in *Fritillaria* are illustrated in Figure 5.⁽⁹⁾

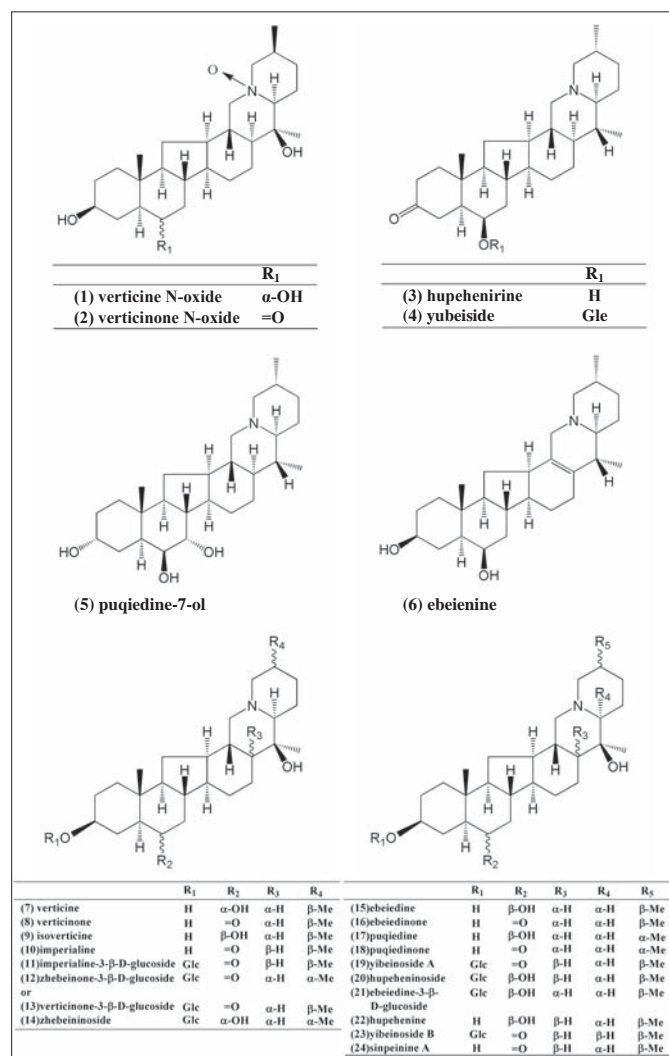


Figure 5: Chemical structures of some steroidal alkaloids isolated from Beimu.

METHODS FOR QUALITATIVE ASSESSMENT OF FRITILLARIA BULBA

Starch is an important polysaccharide consisting of a large number of glucose units joined by glycosidic bonds. The physical properties of the native starch, like crystallinity, morphology and thermal stability are varied significantly. Wang

et al. investigated the physical properties of starches from four *Fritillaria* species by means of fourier transform infrared (FT-IR), X-ray diffractometer (XRD), scanning electron microscope (SEM) and thermogravimetric analysis (TGA). They found that the granule sizes, the shape, the crystal type and the thermal stabilities of the tested samples differed significantly.⁽¹⁰⁾ Jaing et al. isolated starches from maize, *Fritillaria* and Chinese yam and compared their physical properties. After enzymatic hydrolysis, lysates were monitored by SEM, X-ray, FT-IR spectra and differential scanning calorimetry (DSC). The results indicated that starch from different species of Beimu displayed different hydrolysis mechanisms (Figure 6).⁽¹¹⁾

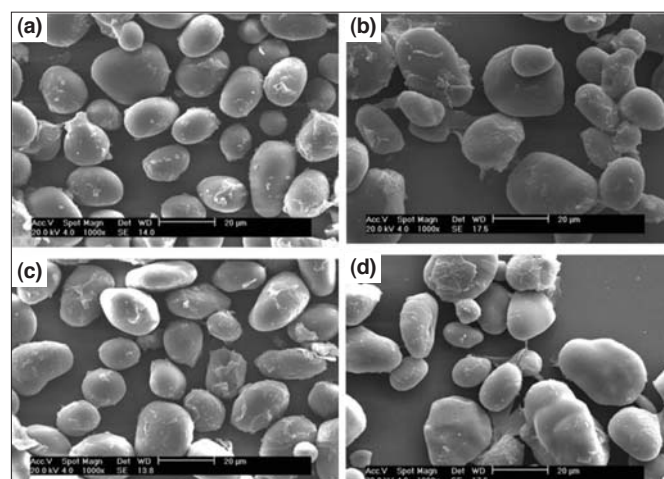


Figure 6. Scanning Electron Micrographs of starches in the hydrolysates of (a) *F. thunbergii*; (b) *F. Ussurensis*; (c) *F. pallidiflora*; (d) *F. cirrhosa*. (Magnification: 500 x) [Adapted from Wang et al.⁽¹⁰⁾]

Both qualitative and quantitative controls of the major active alkaloids in this herb have always been an important issue to ensure its effective and safe clinical uses. A number of studies report morphological and histological methods for differentiation of *Fritillaria* species with different geographical origins.^(12,13) However, due to insufficient distinctive characters within different *Fritillaria* bulbs, such methods could not be performed unambiguously.⁽¹⁴⁾ Improvements in structural characterization of *Fritillaria* alkaloids from complex matrix are urgently needed for understanding their chemical and biological properties.

Thin-layer chromatographic identification of Beimu

Amongst different analytical methods, thin-layer chromatography (TLC) was the first analytical tool developed for qualitative and quantitative study of the major *Fritillaria* isosteroidal alkaloids in Beimu. Developing solvent systems described for elution of the extracts of Beimu include Ethyl acetate-methanol-ammonium hydroxide (17:2:1) system, benzene or cyclohexane-ethyl acetate-diethylamine (6:4:1) system and diethyl ether-ethanol (100:3) system saturated with ammonia vapour. These three solvent systems are the most commonly used mobile systems of TLC of Beimu.⁽¹⁵⁾ However, due to the structural similarity of these isosteroidal alkaloids, many peaks are overlapped and can't be separated well, making TLC methods for simultaneous determination of all steroidal alkaloids in *Fritillaria* very limited use.

A representative chromatogram of TLC fingerprint of Beimu is shown in Figure 7.⁽¹⁶⁾ The samples exhibited several colorful zones in the R_f region from 0.05 to 0.9. Samples 1-4 were characterized by comparison to the standard alkaloids verticine (T₁, R_f = 0.65), verticinone (T₂, R_f = 0.85), imperialine (T₃, R_f = 0.79) and emetine (T₄, R_f = 0.71). Sample 5 shows its main compounds at R_f 0.55 and 0.7. Sample 7 contains significant amount of an unidentified alkaloid at R_f 0.9. Samples 3, 6 and 8 have comparatively lower alkaloid content. Therefore, TLC is a simple and quick method for identification of Beimu.

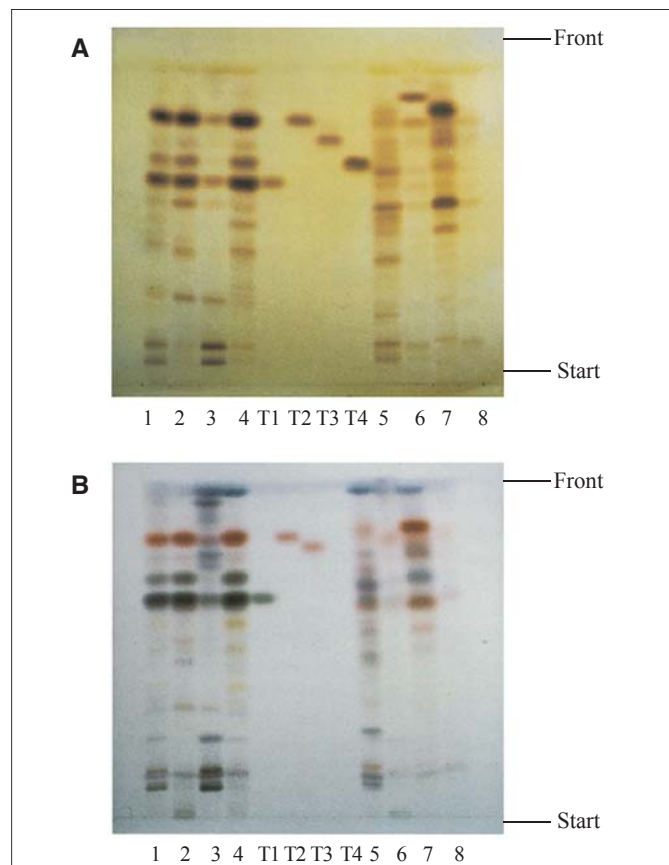


Figure 7. TLC chromatographs of various Beimu extract. Spraying reagent of Plate (A) = dragendorff-reagent; (B) = VS-reagent. Test substances: T1: verticine (R_f = 0.65); T2: = verticinone (R_f = 0.85); T3: imperialine (R_f = 0.79); T4: emetine (R_f = 0.71). Lane 1, 2 = Zhe-beimu (China); 3 = *F. verticillata* var. Thunbergii; 4 = Zhe-beimu (Japan); 5 = Ping-beimu (Jilin, China); 6, 7 = Chuan-beimu (Sichuan, China); 8 = Chuanbeimu (Japan). [adapted from Hildebert Wagner et al.⁽¹⁶⁾]

Liquid chromatographic analysis of Beimu

High-performance liquid chromatography (HPLC) is the most frequently used technique for the analysis of alkaloids because it is low-cost, readily available, and easy to use. However, most alkaloids of *Fritillaria* are non-chromophoric, it's impossible to use UV detection directly without pre- or post-column derivatization.⁽¹⁷⁾ Some studies recommend the use of HPLC coupled with evaporative light scattering detection (ELSD). They reported that ELSD is an excellent detecting method for the analysis of non-chromophoric compounds.^(18,19) Li et al. determined the major biological active isosteroidal alkaloids in *Fritillaria* Bulbus using HPLC–ELSD method with good reproducibility and sensitivity (see Figure 8).⁽¹⁷⁾

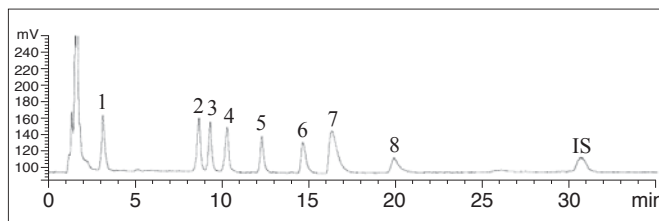


Figure 8. Representative HPLC chromatograms of the extracts of *F. cirrhosa* spiked with standards at the highest concentration in the corresponding calibration range. I.S. = Internal standard; Peak 1 = peimissine; 2 = verticine; 3 = verticinone; 4 = imperialine; 5 = isoverticine; 6 = ebeiedinone; 7 = hupehenine; 8 = ebeiedine. [Adapted from Li et al.⁽¹⁷⁾]

The successful use of liquid chromatography (LC) and time-of-flight mass spectrometry (TOF/MS) for characterizing and determining a wide range of compounds in complex samples suggests LC–TOF/MS a powerful technique for the comprehensive study of multiple steroidal alkaloids in *Fritillaria* extracts with complex matrix.^(20,21) The high resolution property of TOF/MS makes it attractive for performing structural elucidation or confirmation, while the quadrupole mass filter permits fragmentations analysis with accurate mass measurements for both precursor and product ions. Zhou et al. applied LC–TOF/MS method to 26 naturally occurring steroidal alkaloids in *Fritillaria* species, and accurately determined their quantity within 4 ppm error (Figure 9). The excellent selectivity and sensitivity, as well as good linearity, allows identification and quantification of low level of steroidal alkaloids in complex *Fritillaria* extracts.⁽⁹⁾ In addition, Zhou et al. subsequently reported the fragmentation behaviors of steroidal alkaloids from *Fritillaria* species. They proposed some logical fragmentation pathways for different types alkaloids, which are useful for the identification of each alkaloid in these herbal medicines.⁽⁹⁾

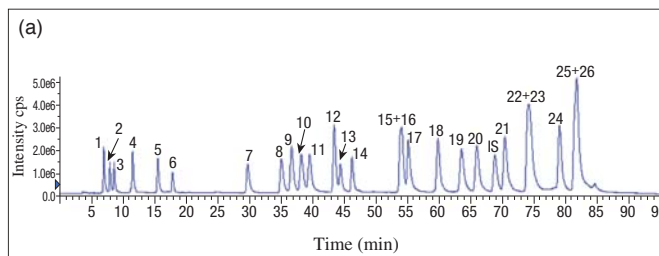


Figure 9. Chromatographic spectrum of standard compounds from *Fritillaria* extracts by means of Total Ion Current. Peak 1 = verticine N-oxide; 2 = puqienine F; 3 = verticinone N-oxide; 4 = puqienine C; 5 = puqienine D; 6 = peimissine; 7 = imperialine-3-β-d-glucoside; 8 = puqienine E; 9 = puqienine B; 10 = puqienine A; 11 = puqiedine-7-ol; 12 = puqietinonoside; 13 = hupeheninoside; 14 = yibeinoside A; 15 = imperialine; 16 = verticine; 17 = N-demethylpuqietinone; 18 = verticinone; 19 = ebeienine; 20 = isoverticine; 21 = puqiedinone; 22 = puqietinone; 23 = puqiedine; 24 = ebeiedinone; 25 = ebeiedine; 26 = puqietinedinone. [Adapted from Zhou et al.⁽²²⁾]

Other methods for analysis of Beimu

There are also molecular biological methods. For example, Ronsted et al. used DNA sequences from the maturase-coding plastid matK gene and the trnK intron, the intron of the ribosomal protein-coding rpl16 plastid gene, and the nuclear ribosomal internal transcribed spacers (ITS) to study the infrageneric relationships within 37 taxa of *Fritillaria*

(Liliaceae).⁽²³⁾ The successful implications mainly depend on the quality of DNA isolated from the processed materials.

BIOLOGICAL ACTIVITIES

Antihypertensive activity

Bioassay-guided fractionation of the BuOH-soluble extract of *Fritillaria ussuriensis* afforded verticinone, verticine, and peimisine and these compounds inhibited angiotensin I converting enzyme activity in a dose-dependent manner, displaying 50 % inhibitory concentration values of 165.0 μM , 312.8 μM , 526.5 μM , respectively.⁽²⁴⁾ Kang et al. reported that intravenous injection of Bulbus *Fritillaria* water extract lowered the mean arterial pressure of anesthetized rats in a dose-dependent manner and increased NO and cGMP productions in intact vascular tissue. The ACE activities and the angiotensin I-induced vasoconstriction were strongly inhibited.⁽²⁵⁾

Anticholinergic activity

Impericine, forticine, delavine, persicanidine A and imperialine were screened for their cholinesterase inhibitory activity using acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), and these compounds showed anticholinergic activity.⁽²⁶⁾ Ebeinone, isolated from *Fritillaria imperialis*, is a muscarinic receptor antagonist that exhibits selectivity for M_2 receptors over M_3 receptors and also shows evidence of allosteric antagonism.^(27,28)

Antitussive, expectorant and anti-inflammatory

Imperialine, imperialine- β -N-oxide, isovorticine, and isovorticine- β -N-oxide isolated from Bulbus of *Fritillaria wabuensis* significantly inhibited cough frequency and increased latent period of cough in mice induced by ammonia.⁽²⁹⁾ Chuanbeinone, verticinone, and verticine were also can inhibit cough frequency and increased latent period of cough in mice, enhanced mice's tracheal phenol red output in expectorant evaluation, and inhibited the development of ear edema in a dose-dependent manner in anti-inflammatory assessment.⁽³⁰⁾

Antifungal activity

Verazine- (veramitaline, stenophylline B, stenophylline B-3-O- β -d-glucopyranoside, veramiline-3-O- β -d-glucopyranoside) and jerveratrum-type (jervine, jervine-3-O- β -d-glucopyranoside) alkaloids exhibited strong antifungal activities against the phytopathogenic fungus *Phytophthora capsici* with MICs of 160, 120, 160, 80, 80 and 120 $\mu\text{g}\cdot\text{L}^{-1}$, and the verazine-type alkaloids stenophylline B, stenophylline B 3-O- β -d-glucopyranoside and veramiline 3-O- β -d-glucopyranoside were shown to also inhibit the growth of another fungal phytopathogen *Rhizoctonia cerealis* with MICs of 160, 120 and 120 $\mu\text{g mL}^{-1}$.⁽³¹⁾

Neuroprotective effect

Xu et al. isolated two labdane diterpenes from the bulbs of *Fritillaria ebeiensis*, and their structures were elucidated as 6 α ,7 β -dihydroxy-labda-8(17), 12(E), 14-triene and 6-oxo-2 α -hydroxy-labda-7, 12(E), 14-triene, on the basis of spectroscopic data analysis (IR, ESI-MS, HR-ESI-MS, 1D and 2D NMR). Both of the isolates showed neuroprotective effects against MPP⁺-induced neuronal cell death in human dopaminergic neuroblastoma SH-SY5Y cells.⁽³²⁾

SIDE EFFECTS/ADVERSE EFFECTS/TOXICITY

Total alkaloids of *Fritillariae Hepehensis* Bulbus were given intraperitoneally to mice, and the LD₅₀ was tested to be 13.71 \pm 1.24 g/kg. If the alkaloids were given orally, the LD₅₀ was 1025 mg/kg. Therefore, The toxicity of the extract of the *Fritillariae Hepehensis* Bulbus was extremely low.⁽³³⁾

DOSAGE AND METHODS OF MEDICATION

The most commonly use of Beimu is that, weigh 3 to 10 gm of raw materials, boil with water and take the extract daily.⁽³⁴⁾

CONCLUSION

Beimu is one of the most ancient and popular herbal medicine used for a broad range of indications. Quite a lot of clinical trials and systematic reviews are now available and shows that the extracts of the herb have antihypertensive activity, anticholinergic activity, antitussive, expectorant and anti-inflammatory, antifungal activity, and neuroprotective effect. In addition, the toxicity of Beimu is proven to be low. The obtained conclusions vary but are still encouraging. Future deep clinical research in this area should be concerned with overcoming the methodological limitations of the previous researches.

Author's background

WANG Yixuan Anna is a research assistant in the Department of Biology and Chemistry, The City University of Hong Kong. She received her BSc trainings in Zhejiang University of Science and Technology, China. **SHEN Qing** is a PhD student at the same institute. He works on a project relevant to the effect of herbal extract on the lipidomic profile of organisms. He received his BSc and MSc trainings in China. **Dr. CHEUNG Hon-Yeung**, who is an associate professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong since 1989, is a manufacturing pharmacist and biotechnologist. He has more than 40 years of work experiences in industries, academic and consultancy jobs. He was an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzhen Government. Dr. Cheung has published more than 220 papers and articles in many prestigious international journals. His email address: bhhonyun@cityu.edu.cn.hk

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SHPHK

Dear pharmacists, friends and colleagues,

I am pleased to invite you to join us in the Hong Kong Pharmacy Conference 2014.

The theme title of the Conference this year is “Breaking New Ground for Pharmacy Service in Primary Care”. With the demographic transition to ageing population together with an increase of life expectancy in Hong Kong and the rest of the world, it is recognised globally that primary healthcare services should be expanded to divert the intense burden exerted on the already over-stressed healthcare system. Pharmacists can make tremendous contributions in this area, as proven many a time in international literatures and we are going to discuss this together at the conference.

The Hong Kong Pharmacy Conference is, as ever, the result of the joint efforts from all pharmacists in Hong Kong, namely the School of Pharmacy of the Chinese University of Hong Kong, the Department of Health, the Hospital Authority, the Department of Pharmacology and Pharmacy of the University of Hong Kong, the Practicing Pharmacists Association of Hong Kong, the Pharmaceutical Society of Hong Kong and the Society of Hospital Pharmacists of Hong Kong.

In order to highlight our theme this year, we are very honoured to have invited Professor Gabriel Leung, a renowned scholar in public health to spark off the discussion on Day 1. Professor Leung shall share his views on the potential of the pharmacy profession in providing and advancing the services in a primary care setting. His speech shall be followed by a plenary session by elites in primary care who shall continue to inspire and enlighten us on the topic.

This global theme will be followed through on Day 2, with a lot more assortments of exciting and relevant topics. We have invited a leading geriatric pharmacist from Australia to share his experience in managing elderly patients in a primary care setting, whereas a pharmacist from the UK shall share his experience on how pharmacists can apply their expertise in providing services in travel medicines. Our local pharmacists from the community pharmacies and medical centres shall update us on the latest models in their practice settings.

On top of the continuation of the conference theme, we also have more specialised themes to cater for the needs of different colleagues. In the designated clinical stream, there is a session on the current management of ADHD, with patients invited in to share us their experience in coping with the disease and the related treatments. By popular demand from last year’s success, we shall continue the therapeutic debates. Practicing clinical pharmacists will debate on controversial topics on pharmacotherapies or practices. The hot topic of biologics, which is transforming the industry of drug development, will also be addressed by renowned overseas pharmacists.

For hospital pharmacy practice and management, we feature quality assurance on the design and implementation of PIC/S GMP facilities in local and overseas settings. The leading experts from the Clinical Trial Centre will speak to us on the running of clinical trials in Hong Kong and the roles of clinical pharmacists in studies; speakers from Singapore, Taiwan and China would share with us the advancements in running automated drug supply in their settings.

The grand finale of the conference would feature a plenary session by our young pharmacists. They will share with us their aspirations of the profession that they dedicate themselves to. Through these young eyes, it provides us with an invaluable opportunity to reflect upon ourselves and our profession – the past, present and future. We hope that this will enable us to see the profession with a different eye, and help us to navigate our profession in the years to come.

Don't miss the opportunity to be part of our conference event to keep abreast of the latest developments in the changing world of pharmacy. I am confident that you would enjoy it very much. See you all in the Hong Kong Convention and Exhibition Centre on 15 and 16 March, 2014.

Yours faithfully,



Professor Ian Wong
Chairperson
Hong Kong Pharmacy Conference 2014

Hong Kong Pharmacy Conference 2014

Date: 15th – 16th March, 2014

Venue: Hong Kong Convention & Exhibition Centre

Breaking New Ground for Pharmacy Service in Primary Care

TENTATIVE Programme

15th March, 2014 (Saturday)

Time	Topics
1:30pm	Registration
2:30pm – 2:40pm	Opening Ceremony
2:40pm – 2:50pm	Welcome Speech by Prof. Ian Wong, Chairman of the Conference
2:50pm – 3:40pm	Keynote & Theme Speech 1 Perspectives on the potential of the pharmacy profession / primary care Prof. Gabriel Leung, Dean, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
3:40pm – 4:10pm	Coffee Break and Poster Exhibition
4:10pm – 4:40pm	Theme Speech 2 The latest development of primary care in Hong Kong Dr. Monica Wong, Head, Primary Care Office, Department of Health, Hong Kong
4:40pm – 5:40pm	Theme Speech 3 Scope of primary care services in Hong Kong Launch of "My eDrug Manager"
7:00pm – 10:00pm	Conference Dinner

16th March, 2014 (Sunday)

Time	I: Primary Care	II: Clinical Pharmacy	III: Informatics, Technology and Pharmaceutics
8:30am – 9:10am	<p>Pharmacists' involvement in primary care for the geriatric population</p> <p>A/Prof. Chris Alderman Director of Pharmacy, Repatriation General Hospital & Interim Director of Mental Health Pharmacy Services, SA Pharmacy, Australia</p>	<p>Therapeutic Debate</p> <p>Topic 1: Antiplatelets</p> <p>Topic 2: Oncology</p> <p>Topic 3: Paediatrics</p>	<p>How useful is automation for centralized in-patient drug distribution system? – sharing of experience</p> <p>Ms. Irene Quay Chief Pharmacist, KK Women's and Children's Hospital Pte Ltd., Singapore</p>
9:10am – 9:50am	<p>Local perspectives on primary care</p> <p>Ms. Catherine Hung Chief Pharmacist, Central Pharmacy, Quality Health Care Medical Services Ltd., Hong Kong</p>		<p>Application of information technology to improve drug safety: the experience of a medical center in Taiwan</p> <p>A/Prof. Fe-Lin Lin Wu Associate Professor and Former Director, Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taiwan</p>
9:50am – 10:30am	<p>New services and developments in community pharmacy: alternative dispensing model</p> <p>Ms. Sylvania Ho Watson's, Hong Kong</p> <p>Mr. Philip Chiu Senior Pharmacist, Mannings Health & Beauty Chain Store, Hong Kong (Language: Cantonese)</p>		<p>PIVAS - the quality control and risk management processes PIVAS的全程質量控制與風險防範</p> <p>Ms. Sun Yan The General Hospital of People's Liberation (301 Hospital)</p> <p>孫燕主任 中國北京人民解放軍總醫院, 解放軍醫學院, 301醫院藥品保障部 (Language: Putonghua)</p>
10:30am – 11:00am	Coffee Break – Poster Exhibition		
11:00am – 11:40am	<p>Research in primary care change by research: influence on government and regulation</p> <p>Prof. Liam Smeeth Head, Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, United Kingdom</p>	<p>Progress and update on biosimilars development in Korea and Asia</p> <p>Dr. Alex Kudrin Medical Assessor, Biological Licensing Division, Medicines and Healthcare Products Regulatory Agency, United Kingdom</p>	<p>Design of a PIC/S GMP biological facility – an experience from Taiwan</p> <p>Mr. Kenny Peng Director, PharmEng Consultancy, Taiwan</p>
11:40am – 12:20pm	<p>Piloting new pharmacy services in primary healthcare</p> <p>Ms. Iris Chang The Practising Pharmacists Association of Hong Kong, Hong Kong</p>	<p>Biologics in chronic arthritis: the role of the pharmacist in the clinical setting</p> <p>A/Prof. Benoit Allenet Clinical Pharmacist / Associate Professor, Grenoble University Hospital, France</p>	<p>Local GMP implementation – step by step</p> <p>Dr. Celine Cheng President, The Hong Kong Pharmaceutical Manufacturers Association, Hong Kong</p>
12:20pm – 2:00pm	Lunch – Poster Exhibition, Multi-media Show		
2:00pm – 2:40pm	<p>Travel medicines for pharmacists</p> <p>Dr. Bonnie Wong Department of Medicine, The Chinese University of Hong Kong, Hong Kong</p>	<p>Advancements in the management of Attention Deficit Hyperactivity Disorder (ADHD)</p> <p>Prof. Ian Wong Head, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong</p>	<p>International drug trials and investigational drug management – past and future</p> <p>Mr. Henry Yau Managing Director, Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong</p>
2:40pm – 3:20pm	<p>Pharmacist-led advanced travel health service</p> <p>Mr. Kit Tse Director, Tse Consulting Limited, United Kingdom</p>	<p>Attention Deficit Hyperactivity Disorder sharing by patient / group</p> <p>ADHD Association, Hong Kong (Language: Cantonese)</p>	<p>Regulatory control of clinical trials in Hong Kong</p> <p>Ms. Christine Cheung Senior Pharmacist, Drug Office, Department of Health, Hong Kong</p> <p>Pharmacists' role in clinical trials in Hong Kong</p> <p>Ms. Linda Cheung Pharmacist, Chief Pharmacist's Office, Hospital Authority, Hong Kong</p>
3:20pm – 5:00pm	<p>Plenary Session: Sharing by Young Pharmacists (Language: Cantonese)</p>		
5:00pm – 5:15pm	<p>Closing Remarks by Ms. Phoebe Chan, Vice Chairlady of the Conference</p>		

*Talks are in English unless otherwise indicated.

The Annual General Meeting of the Pharmaceutical Society of Hong Kong and the 20th Anniversary of the Hong Kong Pharmaceutical Journal

The Annual General Meeting of the Pharmaceutical Society of Hong Kong was held on 14 December 2013 at 6:00 p.m. at the Huthart Room II & President's Room, 3/F South Tower, YMCA in Tsimshatsui. The President, Ms. Mary CHENG reported on the activities for 2013 and the Treasurer, Ms. Candy TAI reported on the financial standing of PSHK. The election of GC members began at around 7:00 p.m. Current year's President and the three Pharmacy & Poisons Board Representatives naturally become GC members for 2014 and 11 General Council members were nominated and were automatically elected without contentious. 13 GC members stayed on and 2 new GC members joined the coming term. The meeting was followed by the AGM of the Joint Pharmaceutical Services Foundation (JPSF) and the motion of adopting the newly elected GCs of PSHK as the members of the GC of this Foundation and the Treasurer Report of JPSF were adopted in the AGM.

Dinner was held immediately after the completion of the 2 AGMs and it was also the celebration dinner of the 20th Anniversary of the Hong Kong Pharmaceutical Journal (HKPJ).

Our Guest of Honour Ms Linda WOO, Assistant Director, Drug Office, Department of Health (DH) gave a welcome speech making reference to the past development and encouraging the profession to continuous the effort to advance forward and the Chief Editor of HKPJ Dr. CHEUNG Hon-yeung shared his past 16 years experience in HKPJ and appealed to fellow pharmacists to actively contribute to this publication which belongs to the profession.

We look forward to a new year of advancement for the Pharmacy profession.

General Council of the Pharmaceutical Society of Hong Kong 2014		
President	Ms. CHENG Mary Catherine	
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Mr. YAU Eric	Mr. LEE Chris	Dr. ZHOU Keary
Ms. YAN Cadence		
Pharmacy & Poisons Board Representatives		
Ms. CHIANG Sau Chu	Mr. KWONG Benjamin	Mr. WONG Andy

*Newly elected GC members (They replaced Peter SUEN and Candy LAU)



Hong Kong Pharmaceutical Journal Editorial Board members: (Back row, from the left) Ritchie KWOK, Phoebe CHAN, Ivy CHAN, Johnny WONG. (Front row, from the left) Candy TAI, Wanda KWAN, Mary CHENG, Dr Hon-yeung CHEUNG, Esther CHAN.



Honored guests with some of the PSHK GC members.



PSHK members at the Annual Dinner



PSHK members at the Annual Dinner



PSHK members at the Annual Dinner

A weekend trip to Taipei with the President of PSHK

reported by Ms S C Chiang*

I am sure many of us know that Mrs Mary Cheng is the President of Pharmaceutical Society Hong Kong but not many would be aware how hard she tries to assume this important leadership role. So, the intention of this report is partly to inform our members about the experience we have gained during our weekend trip to Taipei but more importantly, through reporting, to enable our members to realize how proud we should be to have such a dedicated lady as our President who has such devotion for our Society and the pharmacy profession!

So, the three of us including Mrs Mary Cheng, Janet Pang[#] and I set off on Friday, 11th November 2013 to board the earliest morning flight to Taipei (declaration: we made the trip with all expenses from our own pocket and with formal leave application from our work place). After much chit chatting along the way and several hours later, we found ourselves ready for lunch at a famous restaurant serving typical local Taiwanese food near our hotel in Taipei. Not surprising to those who know about Taiwan, the different varieties of food offered is most interesting and appetizing and of very good value!



Taiwan offers an exciting range of food choices, at very reasonable and affordable prices, much to our surprises and satisfaction! We collected all the name cards as we went from 小籠包, 麻辣火鍋, 擔仔麵 and 粉圓.....to our favourite 鳳梨酥, 太陽餅...

Next, at 2:00p.m., the three of us set off to accomplish one of our major objectives for the trip i.e. to visit National Taiwan University Hospital Pharmacy Department. We were greeted by Dr Fe-Lin Lin Wu who is the Associate Professor of Graduate Institute of Clinical Pharmacy at the College of Pharmacy, National Taiwan University. Dr Wu spent three hours with us explaining in detail about the in-patient drug distribution system for their hospital where a centralised unit dose dispensing system with daily medication carts exchange service by the pharmacy was employed. According to her advice, she repeatedly emphasized that if we have a choice of providing the unit dose dispensing, we must not use this model as the starting point. Dr Wu's experience about this centralised unit dose dispensing system is that pharmacy staff spent far too much time filling the individual medication cabinets and the manual process is labour intensive and is not efficient but pharmacy has to tackle the time pressure to complete the carts filling in order to match each of the drug administration rounds for all the in-patients. For this reason, although they are switching to the new pilot of decentralised unit dose approach using the smart medication cabinets at the ward levels, this is receiving some resistance from the nursing staff who think the old model works better to their convenience.

Dr Wu also showed us the rest of the pharmacy department such as the Aseptic Dispensing areas, the Drug information and clinical pharmacy service, the out-patients department, the repackaging service and even the pharmacy warehouse.

It is worth pointing out that the pharmacy service delivery model has much resemblance to what we know about the US system. This is not surprising as many of the Taiwanese pharmacists would pursue post graduate or doctorate degree in pharmacy in the United States.



Mary, Janet and S C Chiang were greeted by Dr Fe-Lin Lin Wu who Associate Professor of Graduate Institute of Clinical Pharmacy at the College of Pharmacy, National Taiwan University would be our speaker at the upcoming Hong Kong Pharmacy Conference 2014.



NTUH has 21 clinical pharmacists serving 27 units and their Computerised Physician Order Entry system was very comprehensive with various clinical decision features built in.



With the centralized drug distribution system and unit dose dispensing, medication carts have to be refilled daily generating substantial workload for the pharmacy. NTUH has plans to move towards decentralized system with use of smart medication cabinets. They also provide TPN, oncology and PIVAS.



NTUH has a very busy out-patients clinic where patients use the service under insurance coverage and their clinical pharmacists also provide anticoagulant clinics at a charge.



We also saw their automatic warehouse management system which was implemented since May 2009 including the pick to voice system. It was impressive as all expiry dates and batch numbers were bar coded with the GTIN.

Overall, our impression of the NTUH pharmacy is that they are rather similar to our Hong Kong public hospitals in the work load with very busy in-patients and out-patients dispensing service. Even the drugs used and hence the LASA (Look Alike and Sound Alike) drug name pairs and Tall Man lettering are very similar to ours. However, their deployment of IT systems with incorporation of very detail functionalities such as antibiotic stewardship program and clinical pharmacists' intervention documentations at the patients' drug records were good

examples of how well their systems were designed to facilitate the clinical pharmacists' work and are definitely envious of our pharmacists in Hong Kong. They also use automated dispensing machines to do the unit dose drug packaging service and in this area of development, Hong Kong hospitals seem to be more conservative. Also, their pharmacist manpower resources are much more reasonable with a high percentage of them having a doctorate degree or Pharm D degree when compared to Hong Kong, and they do not have the equivalence of the dispenser grades of pharmacy staff in their pharmacy.



After the hospital visit, we met up with Mr Joseph Wang (王文甫) who is the President Elect of the 25th FAPA Congress which will be held in Kota Kinabalu, Sabah, Malaysia between 9 – 12th October 2014 and the theme is Expanding The Pharmacists' Role in Wellness and Sustainable Health. Mr Wang is also an active figure in Taiwan and has done much to help make the mandatory separation of Prescribing from Dispensing (SPD). As Mary has explained before we made this trip, it would be good for us to get to know how our counter parts in other places are doing in enhancing the image of the pharmacy profession and what are their strategies and political struggles to gain more support from the government to implement SPD. Well, with this set as our agenda, the remaining time that we spent with Joseph has definitely been most useful. Apparently, Joseph is a very experienced pharmacist who has made outstanding contribution to the advancement of pharmacy practice in the community side. Thanks to his patience and tolerance, we were briefed about some of the political background and journey our Taiwan pharmacists have travelled in the past before coming to their present state of government policy of separation of prescribing from dispensing. Through our conversation with Joseph, we understood how their medical insurance coverage scheme provided the timing and the opportunity for the pharmacists in the community to set up the pharmacy outlets throughout the Taiwan to serve the medication dispensing needs of the local population. As we listened, we learnt how they have maneuvered and lobbied their political leaders to grant them the independent dispensing practice the experience of which was the most interesting and that we pharmacists in Hong Kong have yet to understand and dare dream about! But at least, we now understand that nothing would be given free from the Government. So, as we envy the Taiwan model, we must also appreciate that our Taiwan pharmacist friends have gone through their local struggles too. If we pharmacists in Hong Kong do not form a united force to speak one common language with one single voice about our future strategic direction, then we can be sure that it would be the status quo with no change at all. Throughout the streets in Taipei, we saw the prominent presence of many community pharmacy outlets and the pharmacists themselves were owners of the outlets with a lot of prescription dispensing and patient counseling activities. For each prescription processed, there is a reimbursement of dispensing fees on top of the medications costs. From what we have observed, the customers were from the neighborhood popping in to have their blood pressure measured and had their medications dispensed.

We could not help asking ourselves: will this scene also happen in Hong Kong? Our visit and our conversation exchange

might have enhanced our understanding about the journey our Taiwan pharmacist friends have travelled, but would this be the same game that we need to play in Hong Kong and if so, who can be our active lead players? All these remain as some unanswered questions that sprang to our minds!



The pharmacist happily smiling is the son of Mr Joseph Wang who has a whole family (his wife, and daughter in law) all working as pharmacist! Depending on patients' needs, the drugs for the same administration time can be packed together in a unit packet using the machine as shown.

Through Joseph, we also learnt that their Pharmaceutical Society has a young pharmacist working full time as the secretary of the society and this young pharmacist, Mr Michael Liu who seemed to enjoy his job a lot as he saw this as an opportunity for him to widen his horizon of the pharmacy profession, was helping Joseph to do a lot of supportive administrative tasks including the organization work for the FAPA Congress. Again, the ability to employ a full time pharmacist staff to serve the pharmacy professional society is something that the PSHK has yet to plan to accomplish.

On the lighter and more fun side of our trip, I must also mention and thank Joseph who drove us around many famous scenic places like 陽明山 and 野柳 and we were taken to lunch and dinner at the most fabulous places to enable us to have a truly good taste of Taipei food!

Finally, we returned to Hong Kong in the late evening on 13th October, Sunday, heavily loaded with so much 手信! I could only say that the entire three days were packed with learning and relearning about the pharmacy practice in Taiwan, both hospital and community, much according to our original plan. If only we could also pay a visit to the nursing homes, that would make an even more perfect visit trip. But this could not be done this time as we could not find the appropriate contact for the visit arrangement. Another important achievement is that we now know Joseph thoroughly well and we will support him as we promise to form a delegation to attend the FAPA Congress (<http://www.fapa2014.com/index.cfm?&menuid=21>) and will meet him there in Sabah again if not sooner.

One final point before this report is finished is my comments about what I have witnessed about our President of PSHK. As a companion to Mary during the trip, I just felt very strongly that Mary has exhibited her passion and leadership even there were just the three of us. The way she has stretched herself to ask and ask again our Taiwan pharmacist friends how this or that was done in Taiwan in order bring about the change in government policy about SPD; how she kept asking for advice about what we need to do in Hong Kong and what plans we need to have, etc. etc. were beyond what I could describe here. I felt very privileged to spend the weekend such as this one with her. Our fellow pharmacists, I just felt that if all of us can do a fraction of what Mary is doing for us, I think we will live to see separation of Prescribing from Dispensing in the community in Hong Kong.

Report written by Ms S C Chiang* on 25th Nov 2013

Ms Janet Pang is the Pharmacy Department Manager of Tung Wah Hospital, Hospital Authority Hong Kong

* Ms S C Chiang is the Senior Pharmacist at the Chief Pharmacist's Office, Hospital Authority Hong Kong and is currently one of the three nominated representatives from PSHK to serve as a member in the Pharmacy and Poisons Board Hong Kong

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ELIQUIS® (apixaban) 2.5 mg & 5 mg Film-coated Tablets Prescribing Information

INDICATION: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA), age ≥ 75 years, hypertension, diabetes mellitus or symptomatic heart failure (NYHA Class ≥ II). **DOSE AND ADMINISTRATION:** Recommended usual dose - 5mg PO BID. Patients with ≥ 2 of the following criteria: serum Cr ≥ 1.5 mg/dL (133 mmol/L), age ≥ 80 years, or body weight ≤ 60 kg, reduce dose to 2.5 mg PO BID. Please refer to full prescription insert for complete details on Dosage and Administration. Eliquis is not recommended in children and adolescents below the age of 18. **CONTRAINDICATIONS:** Eliquis is contraindicated in patients with hypersensitivity to apixaban or to any of the excipients listed in full prescription insert, clinically significant active bleeding, hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Please refer to full prescription insert for complete Contraindications list. **SPECIAL WARNINGS AND PRECAUTIONS:** Please refer to full prescription insert for complete Special Warnings and Precautions. **Haemorrhage risk:** Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs. **Renal Impairment:** No dose adjustment in mild or moderate renal impairment. Reduce dose to 2.5mg PO BID in Patients with severe renal impairment (CrCl 15 – 29 ml/min). Not recommended in patients with creatinine clearance < 15ml/min or in patients undergoing dialysis. **Elderly Patients:** The co-administration of Eliquis with acetylsalicylic acid in elderly patients should be used cautiously because of a potentially higher bleeding risk. **Hepatic Impairment:** Not recommended in severe hepatic impairment. Perform liver function testing before starting Eliquis. **Surgery and invasive procedures:** Discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding or interventions for which the risk of bleeding would be unacceptable. Discontinue at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled. If surgery or invasive procedures cannot be delayed, exercise appropriate caution and weigh bleeding risk against the urgency of intervention. Please see full prescription insert for details. **Laboratory parameters:** Clotting tests (PT, INR, and aPTT) are not recommended to assess the pharmacodynamic effects of Eliquis. **DRUG INTERACTIONS:** Consult full prescription insert for full details on interactions. **PREGNANCY AND LACTATION:** Not recommended during pregnancy. Discontinue breastfeeding or discontinue Eliquis therapy. **UNDESIRABLE EFFECTS:** Please refer to full prescription insert for complete list. **Common:** Eye haemorrhage (including conjunctival haemorrhage), haematoma, epistaxis, gastrointestinal haemorrhage (including haematemesis and melena), rectal haemorrhage, gingival bleeding, haematuria, contusion. **Uncommon:** hypersensitivity (including skin rash, anaphylactic reaction and allergic oedema), brain haemorrhage, other intracranial or intraspinal haemorrhage (including subdural haematoma, subarachnoid haemorrhage, and spinal haematoma), intra-abdominal haemorrhage, haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage, abnormal vaginal haemorrhage, urogenital haemorrhage, application site bleeding, occult blood positive, traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage. **Rare:** Respiratory tract haemorrhage (including pulmonary alveolar haemorrhage, laryngeal haemorrhage and pharyngeal haemorrhage), retroperitoneal haemorrhage. Adverse events should be reported. Adverse events should also be reported to Bristol-Myers Squibb Pharmaceuticals Ltd Medical Information on medinfo.hongkong@bms.com directly or via phone at the following toll free number for HK 3002 7890 and for Macau 0800348

Consult full prescription insert prior to prescribing.

References: 1. Data on file, Bristol-Myers Squibb. 2. Granger CB, Alexander JH, McMurray JJ, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–992. 3. Connolly SJ, Ezekowitz J, Joyner C, et al; for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806–817.



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EU130139/AUG

NEW INDICATION

ACTILYSE® (Boehringer Ingelheim)

Active Ingredient:

1 vial with powder contains 50 mg alteplase (corresponding to 29,000,000 IU),

Presentation:

Pack with 1 vial containing 50mg of the active ingredient and 1 vial with 50 ml water for injections.

Pharmacological Properties:

The active ingredient of Actilyse is alteplase, a recombinant human tissue-type plasminogen activator, a glycoprotein, which activates plasminogen directly to plasmin. When administered intravenously, alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

Indications:Thrombolytic treatment in acute myocardial infarction

- 90 minutes (accelerated) dose regimen: for patients in whom treatment can be started within 6 h after symptom onset

- 3 h dose regimen: for patients in whom treatment can be started between 6 - 12 h after symptom onset provided that the diagnosis has been clearly confirmed.

Actilyse has proven to reduce 30-day-mortality in patients with acute myocardial infarction.

Thrombolytic treatment in acute massive pulmonary embolism with haemodynamic instability

The diagnosis should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning. There is no evidence for positive effects on mortality and late morbidity related to pulmonary embolism.

Fibrinolytic treatment of acute ischaemic stroke

Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Dosage & Administration:Myocardial infarction

- a) 90 minutes (accelerated) dose regimen for patients with myocardial infarction, in whom treatment can be started within 6 hours after symptom onset: 15 mg as an intravenous bolus, 50 mg as an infusion over 30 minutes, followed by an infusion of 35 mg over 60 minutes until the maximal dose of 100 mg. In patients with a body weight below 65 kg, 15 mg as an intravenous bolus, and 0.75 mg/kg body weight (bw) over 30 minutes (maximum 50 mg), followed by an infusion of 0.5 mg/kg body weight (bw) over 60 minutes (maximum 35 mg)
- b) 3 h dose regimen for patients, in whom treatment can be started between 6 and 12 hours after symptom onset: 10 mg as an intravenous bolus, 50 mg as an infusion over the first hour, followed by infusions of 10 mg over 30 minutes until the maximal dose of 100 mg over 3 hours. In patients with a body weight below 65 kg the total dose should not exceed 1.5 mg/kg. The maximum dose of alteplase is 100 mg.

Pulmonary embolism

A total dose of 100 mg of alteplase should be administered in 2 hours. 10 mg as an intravenous bolus over 1 - 2 minutes, followed by an intravenous infusion of 90 mg over 2 hours. The total dose should not exceed 1.5 mg/kg in patients with a body weight below 65 kg

Acute ischaemic stroke

Treatment must only be performed under the responsibility and follow-up of a physician trained and experienced in neurovascular care.

The recommended dose is 0.9 mg alteplase/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10 % of the total dose administered as an initial intravenous bolus.

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with Actilyse administration and so it should not be administered

Forensic Classification:

P1S1S3

NEW PRESENTATION

ENANTONE® 6 MONTH DPS 30MG (Takeda Pharmaceuticals (HK) Ltd.)

Active Ingredient:

1 dual chamber prefilled syringe contains 30mg of leuprorelin acetate

Presentation:

Dual Chamber Prefilled Syringe.

Pharmacological Properties:

Leuprorelin acetate, the active ingredient in ENANTONE®, is a synthetic analogue of the naturally occurring hypothalamic releasing factor, LHRH, which works to control the release of the gonadotrophic hormones LH (luteinizing hormone) and FSH (follicle-stimulating hormone) from the anterior pituitary gland. In contrast to the physiological LHRH released from the hypothalamus in a pulsatile mode, leuprorelin acetate, also known as an LHRH agonist, works to block the LHRH receptors of the pituitary gland with chronic therapeutic use, and after an initial short-term stimulatory effect, causes them to become "desensitized" ("down-regulated"). As a consequence, reversible pituitary suppression of gonadotropin release occurs, followed by a decrease in testosterone levels, thereby influencing the growth of prostate cancer, which is normally stimulated by dihydrotestosterone (DHT) formed by reduction of testosterone in the prostate cells

Indications:

For the treatment of advanced prostate cancer.

Dosage & Administration:

ENANTONE® 6 MONTH DPS is to be administered subcutaneously once every six months.

Forensic Classification:

P1S1S3

TIME SAVING LIFE CHANGING

Enantone 6 Month DPS

for prostate cancer*:

Introducing a new delivery system



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